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Original Article

Synergistic Effect Of Passive Cigarette Smoke On Spleen And Bone Marrow Of Fractionated Low-Dose Whole Body X-Irradiated Albino Rats

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synergistic effects,
cellular damage.

ABSTRACT

Introduction: Passive cigarette smoke causes cellular damage and even death. While ionizing radiation has been used in various fields, a combination of passive cigarette smoke and ionizing radiation has been linked to the development and exacerbation of countless diseases. In this perspective, the effect of passive cigarette smoke and fractionated low-dose whole-body X-irradiation totaling 0.83Gy on Albino rats were investigated. Methods: The rats were divided into four groups and exposed to fractionated low-dose whole-body X-irradiation for 3 days (total of 0.82Gy), passive cigarette smoke, or both in a smoke machine model for 28 days. Histological examinations of the spleen and bone marrow of euthanized rats were performed to investigate cellular changes in the haematopoietic system. Results: The results showed progressive hyperplasia of white pulps, regression of red pulp, constriction of the central vein in the spleen, and the onset of progressive mild hypocellularity of the bone marrow, indicative of mild aplastic anaemia. These effects were observed with marked severity in the group exposed to both radiation and cigarette smoke. Conclusions: This study demonstrated the deleterious effect of passive cigarette (second-hand) smoke and X-irradiation on the spleen and bone marrow, necessitating the control of tobacco and X-irradiation exposure.

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Introduction

With the increased application of ionizing radiation in the modern world, underseeing its benefits regarding dose and method of exposure is of vital importance, especially since the overall cost incurred from radiation exposure like other agents (e.g., drugs) by intent or by accident can be measured in the premise of its after-effects and its interaction with other factors (e. g, cigarette smoke, alcohol) in an individual's health [1,2,3,4,5,6]. It is a known fact, that where there is an active smoker, there are often passive smokers to share in the spoils won from burning each stick of cigarette.

Whole-body irradiation (total body irradiation-TBI) is an exposure of the entire body rather than an isolated part to radiation with a resultant uniform distribution of a radioisotope throughout the body tissues and cells [7]. Fractionated whole-body irradiation involves dividing a desired cumulative dose into smaller doses administered over several sessions to reduce its toxic effects on healthy cells.

However, the response of an organism to TBI is determined by the combined response of all systems in the body [8]. The extent of cellular and tissue response to radiation injury depends on the ionizing radiation and target organ [8].

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An individual who breathes in the smoke from a primary smoker, i.e., second-hand smoke (SHS) is called a passive smoker or second-hand smoker [9]. Cigarette smoking continues to be a major public health concern ([10,11,12], despite the awareness of the numerous health implications associated with it especially in the third world face of harsh economic conditions [13].

There are no known safe levels of SHS [14,15]. Being a complex mixture of about 7000 chemicals, with over 50 of which are implicated to be carcinogens [16], exposure to SHS can either trigger or worsen symptoms of diseases [9,17]. Reports of its synergism with other risk factors (e.g. radon gas) in initiating or aggravating disease have been stated in the US Surgeon General report [18].

Unlike the liver, the spleen is highly radiosensitive [19]. Major effects are seen with very low irradiation dose [20,21,22] and moderate irradiation dose [23], showing a sort of radiation hormesis, marked congestion and haemorrhages, marginal zones revealing depletion of their cellular contents, especially from macrophages and lymphocytes [23], degeneration of the white pulps [24] and decrease in spleen weight [25].

The symbolic significance of the spleen and bone marrow in immune and extramedullary haematopoietic prowess has been retold in several studies [26,27]. Passive cigarette smoke has been shown to have a significant impact on bone health, with studies in rats indicating decreased bone mineral density, changes in bone structure, and a decrease in marrow cells and osteoblasts [28]. This study examined the coaction effect between passive cigarette smoke and whole-body X-irradiation on the spleen and bone marrow.

MATERIAL AND METHODS

Experimental Animals

Thirty-seven albino rats (Rattus norvegicus) of varied weights ranging between 180-250g and sexes, aged between 6-10 weeks old were used for the study. They were allowed for one week to acclimatize under standard laboratory conditions. The animals were fed with chow and water ad libitum. Animals were divided into four groups (A, B, C, and D); consisting of 10 rats per group save the control group which consisted of 7 rats, 5 males and 5 females in separate cages constituted a group in compliance with accepted standards for animal caging, and the average weight of each group was taken.

Animal Welfare Provision and Ethical Considerations

This study was conducted according to the current National Academy of Science [29] guidelines for animal welfare. The protocol was reviewed, and the Animal House Department of the University of Jos, Plateau State issued ethical clearance for animal use.

Cigarette dose

1 stick of Cigarette/day of Benson and Hedges brand (1.0 mg of nicotine, 10 mg of tar, and 10 mg of carbon monoxide) was given to each animal per day.

Radiation facilities

Whole body X-irradiation of rats was carried out at the Radiology department, Jos University Teaching Hospital, Jos, Plateau State, using GE Medical System RAD-12 X-Ray Tube Model – 2226680 X-ray machine. A trained Radiology Scientist conducted this procedure. Animals were irradiated at a radiation total dose of 0.82Gy, delivered at a fractionated dose of 30.5mGy for each exposure for 3 days i.e. (Day 1: 10 exposures; Day 2: 10 exposures and Day 3: 7 exposures), Kilovoltage of X-ray: 150Kv, Voltage of tube: 250MAS, Source to target distance: 90cm.

Experimental design

Animals were randomly allocated to test and control groups, a total of four groups (A, B, C, and D). The weight of each animal was measured using a weighing scale and the average weight of each group was taken at the beginning and through the study weekly [30]. At the start of the study, two rats from group A were euthanized according to the Helsinki Declaration to obtain a baseline for the study. Rats in group B and group D were exposed to whole-body radiation at a radiologic laboratory.

Group C and Group D were then exposed to passive cigarette smoke, and as the study progressed two (2) rats were euthanized each week to evaluate the histopathological change.

Sacrifice, Tissue Processing, Staining and Microscopy

All animals were painlessly sacrificed under chloroform anesthesia and subjected to standard necropsy procedures. All tissue samples were fixed in 10% formal saline for 48 hours and processed using appropriate paraffin wax processing techniques of dehydration, clearing, and infiltration. Slides of thin tissue sections of 5µm were made, stained, and examined microscopically. General morphology of liver and spleen sections was demonstrated by the haematoxylin and eosin technique [31], more so, the presence and distribution of iron deposits in the spleen were described by Perl's Prussian blue method [32]. Leishman stain was used to demonstrate the cellular morphology of the bone marrow.

Microscopy

Photomicrographs were taken with a Nikon XSP-106 microscope digital camera system using X10 and X40 objectives.

Statistical analysis

Values are given as means ± the mean's standard error (S.E.). Data collected were analyzed using SPSS Windows version 20.0 software. Microsoft Word 2016 was used to analyze the mean values of the weight of the rats, and food and water consumption during the experiment as bar charts and flow charts.

RESULTS

General observations

Table 1: Showing the general observations of the animals during the period of the experiment

Group	Treatment(s)	Physical and behavioural observations	
1	Control	Smooth fur appearance, rats were active with normal eye colour, normal urine production	
2	WBI only	Smooth fur appearance, less active compared to control, normal eye colour, normal urine production even after whole body radiation.	
3	PCS only	After circadian exposure	Rough fur appearance, less active, sluggish, moderately normal urine output, moderately soft faeces output.
		During exposure	Sudden struggling outlook, increase salivation and tearing, increase fatty faeces output and urine production.
		Just after exposure	Decrease alertness, abrupt sluggishness, decrease salivation and tearing, loss of appetite for food and water.
4	WBI+PCS	After circadian exposure	Following radiation exposure and subsequent PCS exposure, animal had rough fur appearance, were least active, sluggish, moderately normal urine output, moderately soft faeces output.
		During exposure	Sudden struggling outlook, increase salivation and tearing, increase fatty faeces output and urine production.
		After exposure	Decrease alertness, abrupt sluggishness, decrease salivation and tearing, loss of appetite for food and water.

Other physical observations

After the first week of exposure to PCS, animals in group 3 (PCS only) and group 4 (WBI+PCS) were extremely hostile with seeming annoyance once placed inside the smoke tank of the smoking machine even in the absence of a lit cigarette. Hostility increases about 5-10 seconds after a cigarette is lit. Some of the animals quickly position their nose at vents positions (for ventilation) to access air from the environment after minutes of effortless struggle and aggression to come out of the smoke machine.

Graphical representations

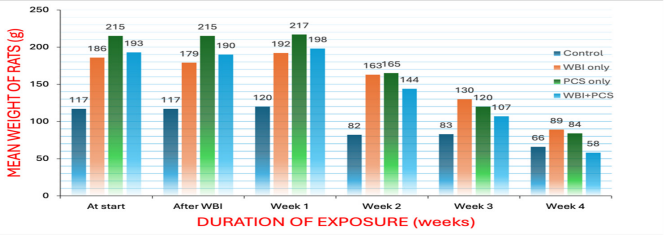


Figure 2: Flow chart showing rats' mean water consumption (Cl) throughout the experiment in various treatment groups.

Key: Group 1: Control; Group 2: WBI exposure only; Group 3: PCS exposure only; Group 4: WBI + PCS exposure

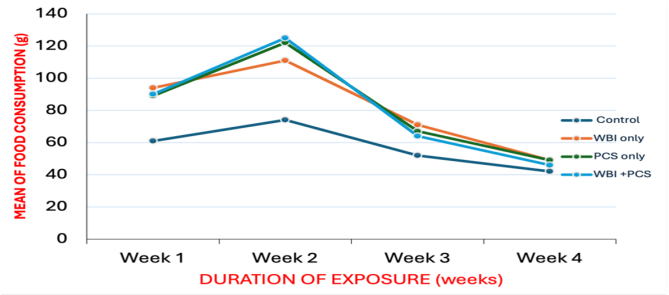


Figure 3: Flow chart showing rats' mean food consumption (g) throughout the experiment in various treatment groups.

Key: Group 1: Control; Group 2: WBI exposure only; Group 3: PCS exposure only; Group 4: WBI + PCS exposure

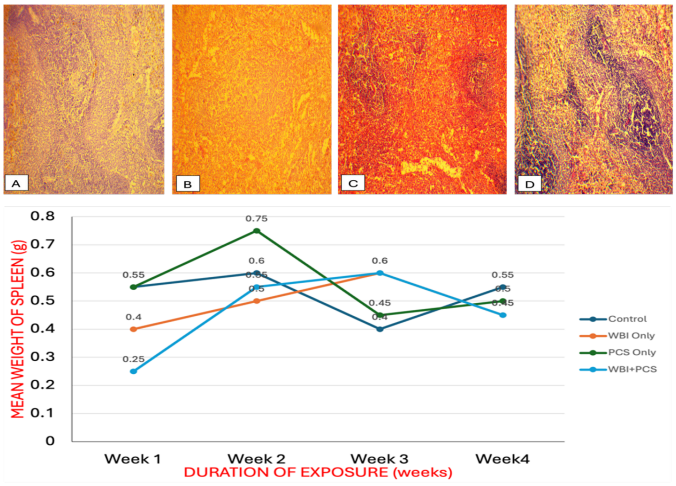
Figure 4: Flow chart showing mean weight (g) of the splenic organ of rats throughout the experiment in various treatment groups.

Group 1: Control

Group 2: WBI exposure only

Group 3: PCS exposure only

Group 4: WBI + PCS exposure

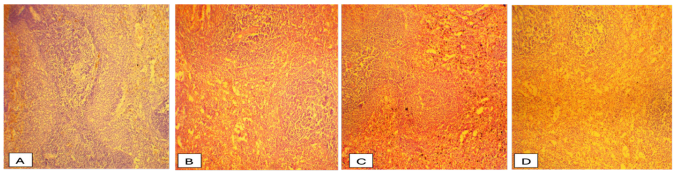


WEEK 1

Plate 1: (A): Spleen histologic section of the control group showing normal splenic tissue consisting of large white pulps encompassing the artery. Large white pulp separated by a wide area of red pulp. Central areas are identifiable in the white pulp. (B): Spleen section of G2 showing splenic pulps not as prominent as control with the incidence of vacuoles suggesting fatty accumulation.

(C): Spleen section of G3 showing red and white pulps is stricken with marked incidence of vacuoles, congested splenic veins, and hyperplasia of the red pulp. (D): Spleen section of G4 showing the marked incidence of vacuoles, fatty changes, and congested central vein.

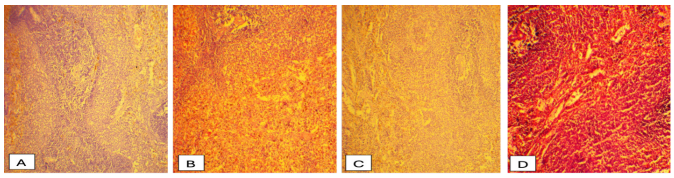
Magnification x100, H&E staining.



WEEK 2

Plate 2: (A): Spleen histologic section of the control group showing normal splenic tissue consisting of large white pulps encompassing the artery. Large white pulp separated by a wide area of red pulp. Central areas are identifiable in the white pulp. (B): Spleen section of G2 showing increased incidence of interstitial vacuoles, and progressive increase in the number and sizes of the lymphoid nodules. (C): Spleen section of G3 showing fewer interstitial vacuoles, slight regression of the red pulp, and progressive increase in the number and sizes of the lymphoid nodules compared to the irradiated group. (D): The spleen section of G4 shows reduced sizes of white pulps, hyperplasia of the red pulp, and increased incidence of vacuoles in the red pulp.

Magnification x100, H&E staining.

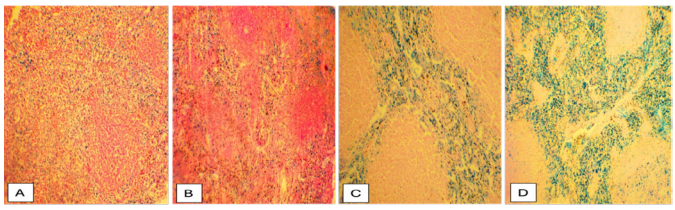


WEEK 4

Plate 4: (A): Spleen histologic section of the control group showing normal splenic tissue consisting of large white pulps encompassing the artery. Large white pulp separated by a wide area of red pulp. Central areas are identifiable in the white pulp. (B): Spleen section of G2 histology remarkably distorted by several clusters of vacuoles. The normal predominance of red pulp. (C): Spleen histological section of G3 minimally affected by vacuolation, red pulp regression, and white pulp hyperplasia with prominent germinal centres. (D): The spleen section of G4 shows marked regression of red pulp, hyperplasia of white pulps with prominent germinal centres, and increased vacuolation in the red pulp.

Magnification x100, H&E staining.

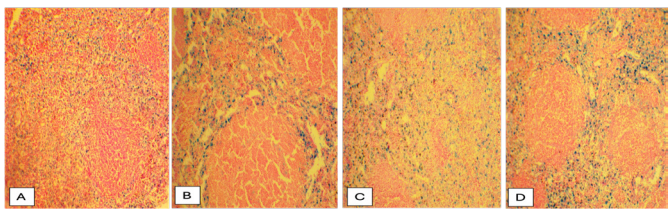
PHOTOMICROGRAPH OF SPLEEN (Perl's Prussian Blue Method)



WEEK 1

Plate 5: (A): Spleen histologic section of the control group showing the presence of few iron deposits in the red pulp which is normal for the spleen. (B): Spleen section of G2 showing the presence of few iron deposits. (C): The spleen section of G2 shows more iron deposits which are localized in the red pulp. (D): Spleen section of G4 showing the presence of increased iron deposits which are more localized in the red pulp and diffused in the white pulp.

Magnification x100, PPB staining.



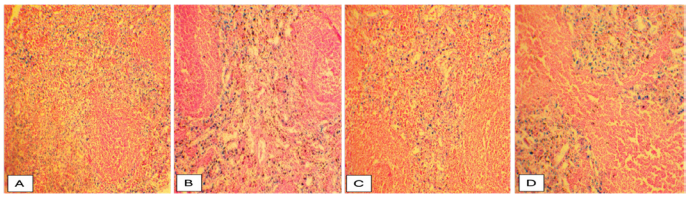
WEEK 2

Plate 6: (A): Spleen histologic section of the control group showing the presence of few iron deposits in the red pulp which is normal for the spleen.

(B): Spleen section of G2 showing the presence of localized increase iron deposits in the red pulp. (C): Spleen section of G3 showing diffused iron deposits.

(D): Spleen section of G4 showing the presence of increased iron deposits

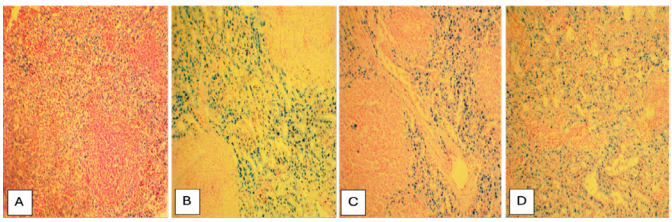
Magnification x100, Perl's Prussian Blue staining.



WEEK 3

Plate 7: (A): Spleen histologic section of the control group showing the presence of few iron deposits in the red pulp which is normal for the spleen.

(B): Spleen section of G2 showing the presence of dispersed iron deposits in the red pulp. (C): Spleen section of G3 showing the presence of dispersed iron deposits in the red pulp. (D): Spleen section of G4 showing the presence of iron deposits which have started infiltrating the white pulp and vacuoles.



Magnification x100, PPB staining.

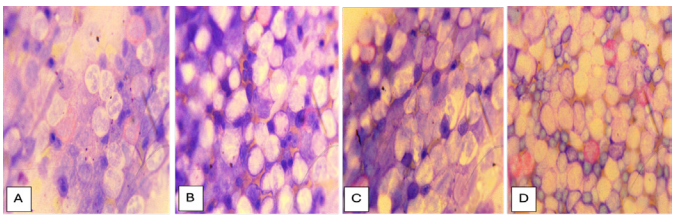
WEEK 4

Plate 8: (A): Spleen histologic section of the control group showing the presence of few iron deposits in the red pulp which is normal for the spleen.

(B): Spleen section of G2 showing the presence of dense iron deposits localized to the red pulp. (C): Spleen section of G3 showing the presence of increased iron deposits in the red pulp and trabeculae.

(D): Spleen section of G4 showing the presence of dense iron deposits which are generalized in the white pulp and red pulp and marked interstitial vacuoles suggesting fatty changes.

Magnification x100, Perl's Prussian Bluestaining.



PHOTOMICROGRAPH OF BONE MARROW

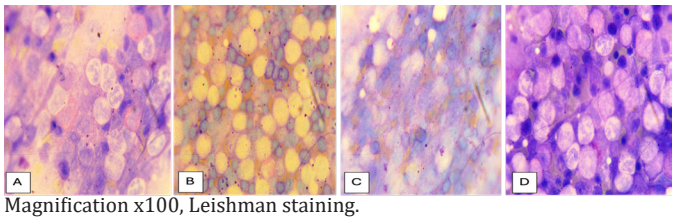
WEEK 1

Plate 9: (A): The bone marrow histologic section of the control group shows numerous basophils, matured and immature neutrophils, several lymphocytes, fewer erythroblasts, and few fat cells.

(B): Bone marrow section of G2 showing numerous fat cells, erythrocytes, several lymphocytes, reduced neutrophils, and few eosinophils.

(C): Bone marrow section of G3 showing few lymphocytes, increased neutrophils, and increased fat cells with few erythroblasts.

(D): The bone marrow section of G4 shows increased fat cells, increased eosinophils, several lymphocytes, and a few erythroblasts.



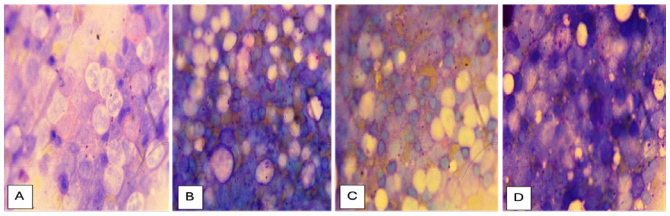
Magnification x100, Leishman staining.

WEEK 2

Plate 10: (A): The bone marrow histologic section of the control group shows numerous basophils, matured and immature neutrophils, several lymphocytes, fewer erythroblasts, and few fat cells.

(B): Bone marrow section of G2 showing fat cells, decreased eosinophils, predominant neutrophils, and several lymphoblasts.

(C): Bone marrow section of G3 showing predominant fat cells, several lymphocytes, and RBCs. (D): Bone marrow section of G4 predominant fat cells with several lymphocytes and lymphoblast, increased neutrophils,



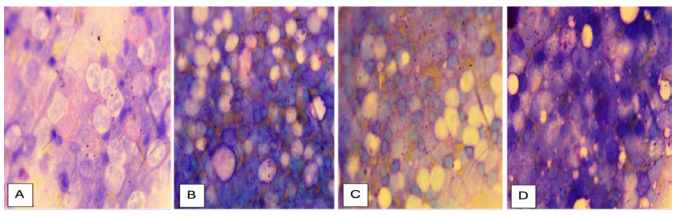
hyper-segmented neutrophil.

Magnification x100, Leishman staining.

WEEK 3

Plate 11: (A): The bone marrow histologic section of the control group shows numerous basophils, matured and immature neutrophils, several lymphocytes, fewer erythroblasts, and few fat cells. (B): Bone marrow section of G2 showing predominant lymphocytes, many fat cells, and some RBCs.

(C): Bone marrow section of G3 showing predominant lymphocytes, several fat cells, and some RBCs. (D): Bone marrow section of G4 showing predominant fat cells, several lymphocytes, and lymphoblast.



Magnification x100, Leishman staining.

WEEK 4

Plate 12: (A): The bone marrow histologic section of the control group shows numerous basophils, matured and immature neutrophils, several lymphocytes, fewer erythroblasts, and few fat cells.

(B): The bone marrow section of the G2 group shows predominant fat cells, several lymphocytes, and some erythroblasts.

(C): Bone marrow section of G3 showing an increase in fat cells, the presence of megakaryocytes, mild increase in lymphocytes. (D): Bone marrow section of G4 showing decreased lymphocytes, and increased presence of neutrophils.

Magnification x100, Leishman staining.

DISCUSSION

A study of the potential damaging synergy of the effects of PCS and X-ray irradiation was undertaken. The experiment design provided a structure that provided a template to compare various treatments across the control and treated groups. Several general observations were made during the experiment (Table 1). The four appearances of the rats, which is the first indication of discomfort in the animal model, were consistently disrupted throughout the experiment in all treatment groups except in the group exposed to WBI only. However, this category of rats lost their agility and became sluggish. Other observations which include restlessness especially on exposure to PCS, tearing and salivation, loss of appetite for food, and reduced water intake, all point to the immediate effects of the two treatments. During the experiment, there was a noticeable decrease in urine output and changes in the texture of their faecal droppings. All these contrasted with the observations on the control group.

The mean weights of the rats in the various treatment groups during the experiment (Figure 1) showed a noticeable reduction in mean body weights beginning in week 2 and steadily progressed in all groups up to week 4. There was a slight decrease in that of the controls also but not as significant as that of the other groups. This shows that WBI, PCS, and a combination of WBI and PCS affected the body weights. These findings agreed with earlier studies [33,34,35,36]. This significant body change was associated with their decreased food and even water intake (Figures 2 and 3). The mean weight of the spleen organs was mildly affected in the experimental groups (Figures 4 and 5).

The general morphology of the spleen's histology and the assessment for iron deposition were used to assess the impact of the treatments on the animals' spleen (Plate 5-8). Within the experimental group, a noticeable increase in the size of the white pulp was observed, coinciding with a progressive depletion of the red pulp. During the experiment from week 1 to 4, there was a significant narrowing of the splenic vein, suggesting tissue injury. Additionally, there was noticeable shrinkage of the red pulp, mild overgrowth of the white pulp with prominent germinal centres, and increased interstitial vacuoles. These findings suggest that the persistent effects of WBI and PCS induce inflammatory reactions in the spleen [37,38].

The Perl's Prussian blue staining revealed the distribution of hemosiderin in the experimental group (Plate 5-8). The study observed a gradual increase in iron deposits and dispersal as the experiment progressed from week 1 to week 4. This pattern was accompanied by the depletion of the red pulp among the experimental groups, particularly the WBI+PCS group. This finding supports previous research indicating that cigarette smoke and radiation can influence and modulate the breakdown of blood cells in the spleen, indirectly impacting mechanisms of blood cell production and causing increased iron release in the peripheral blood and the spleen [39].

The bone marrow is known for its sensitivity to radiation and cigarette smoke, majorly because of the abundant cellular populations of haemopoietic relevance [40]. Overall, the bone marrow smears of the experimental groups showed a decrease in erythropoietic and granulopoietic activity supported by an increase in fat cells and a mild increase in lymphopoietic activity especially in group 4 (Plate 9-12). Hyper-segmented polymorphonuclear leukocyte pools were also present in the experimental group, suggesting the onset of aplastic anemia, which supports the findings of Ajiro et al [28] and Terashima et al., [40].

CONCLUSION

The results of this study show that the coaction of passive cigarette smoke exposure and fractionated low-dose whole-body X-irradiation results in significant systemic effects, particularly in the spleen and bone marrow of Wistar rats. Histologic damage was noted in rats exposed to either passive cigarette smoke or low-dose whole-body X-irradiation, with substantial exacerbation observed in rats exposed to both. Prolonged passive cigarette smoke exposure with or without the exposure of X-irradiation is predictive of severe organ dysfunction, as evidenced by the hypocellularity of the bone marrow and the potential onset of aplastic anaemia.

This research underscores the potentially lethal impact on organ function that arises from any radiation exposure scenario when combined with passive cigarette smoke. It also provides supporting evidence that passive smokers face almost the same risk as active smokers. Moreover, it emphasizes the need for further investigation into the potential synergistic effects of WBI and PCS as risk factors in disease studies, particularly in cancer research and public health considerations.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Availability of data and material: Data are available from the corresponding author upon request

Competing interests: The authors declare no conflict of interest

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