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Original article

Cyclophosphamide-Induced Gastric Histopathological Alterations in Golden Hamsters

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Abstract
Cyclophosphamide is a widely used chemotherapeutic and immunosuppressive agent, but its gastric toxicity remains poorly characterized. This study investigated dose-dependent histopathological changes in the gastric mucosa of golden hamsters following cyclophosphamide administration. Twenty-seven adult female hamsters were divided into control and treatment groups. Animals received intraperitoneal doses of 100 or 200 mg/kg cyclophosphamide on alternating days for one week. Gastric tissues were harvested, fixed in formalin, processed by paraffin embedding, and stained with Hematoxylin and Eosin (H&E) and Periodic Acid-Schiff (PAS) for microscopic evaluation. Histological examination revealed progressive mucosal damage with increasing doses, ranging from mild epithelial alterations at 100 mg/kg to severe disruption, inflammatory infiltration, and reduced mucopolysaccharide secretion at 200 mg/kg. Cyclophosphamide induces dose-dependent gastric injury in golden hamsters, underscoring the importance of histological monitoring during therapy. The model provides a relevant preclinical platform for studying chemotherapy-induced gastric toxicity.
Keywords. Cyclophosphamide, Gastric Mucosa, Histopathology, Golden Hamster.

Introduction

Cyclophosphamide, an alkylating agent, is extensively employed in the management of malignancies and autoimmune disorders due to its potent cytotoxic and immunosuppressive properties [1-4]. Despite its therapeutic efficacy, cyclophosphamide is associated with systemic toxicities affecting multiple organs, including the liver, kidneys, and gastrointestinal tract [5-7]. Histopathological studies have documented dose-dependent tissue damage characterized by inflammation, necrosis, and architectural disruption. While hepatic and renal toxicities are well established, the specific effects of cyclophosphamide on the gastric mucosa remain insufficiently explored. The stomach, as a primary site exposed to circulating metabolites, plays a critical role in digestion and barrier protection.

Chemotherapy-induced gastric injury can lead to mucositis, ulceration, impaired nutrient absorption, and increased susceptibility to infection [8,9]. Current literature provides limited and inconsistent data on gastric toxicity, often focusing on other gastrointestinal segments. Variability in experimental models further complicates extrapolation to clinical practice. Therefore, controlled studies using standardized animal models are essential to elucidate the dose-dependent gastric effects of cyclophosphamide [10-13]. This study aimed to investigate the histopathological effects of cyclophosphamide on the gastric mucosa of golden hamsters, with emphasis on dose-dependent injury patterns. The objectives of this study were to characterize the structural alterations occurring in gastric tissue following the administration of different doses of cyclophosphamide and to evaluate the extent of mucosal injury through detailed histological examination.

Methods

Twenty-seven adult female golden hamsters (150–250 g) were obtained from a local farm in El-Bayda, Libya. Animals were housed in the animal facility of the Histology Department, Faculty of Medicine, University of Benghazi, under controlled conditions. Ethical approval was granted by the Animal Ethics Committee of the University of Benghazi, and all procedures adhered to humane care guidelines. Cyclophosphamide powder was purchased from a local pharmacy, dissolved in physiological saline (50 ml), and administered intraperitoneally.

Animals were divided into control and treatment groups. Treatment groups received doses of 100 mg/kg or 200 mg/kg body weight on alternating days (Day 1, Day 3, Day 5) for one week. At the end of the experiment, animals were sacrificed, and stomach tissues were harvested. Samples were fixed in 10% neutral buffered formalin, processed by paraffin embedding, and sectioned. Histological staining was performed using Hematoxylin and Eosin (H&E) to assess tissue architecture and Periodic Acid-Schiff (PAS) to evaluate mucopolysaccharide content. Stained sections were examined under a light microscope at the University Medical Center's histopathology laboratory.

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Results

Histological examination of the control hamster stomach revealed a well-preserved gastric architecture. The wall consisted of the typical four layers: mucosa, submucosa, muscularis externa, and serosa. The mucosa was lined by simple columnar epithelium with organized gastric pits containing parietal and chief cells in the corpus and mucus-secreting cells in the antrum. PAS staining highlighted abundant mucopolysaccharides and glycoproteins, confirming intact mucin production. No evidence of inflammation, dysplasia, or pathological alterations was observed (Figure 1).

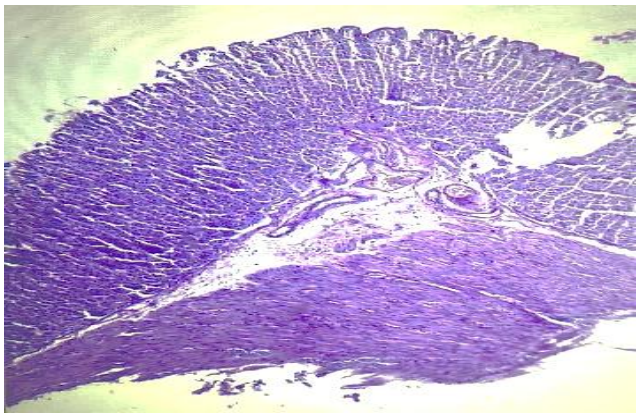

Figure 1. Histological section of control hamster stomach after intraperitoneal saline injection, stained with H&E (×40).

At 100 mg/kg, the gastric structure remained largely intact, with minimal changes. The mucosal, submucosal, muscular, and serosal layers retained normal organization. PAS staining confirmed mucopolysaccharide presence, with a slight increase in mucus secretion in localized areas, but without pathological significance. However, focal mucosal erosion and mild epithelial degeneration were noted, accompanied by occasional vacuolization and apoptotic changes. Moderate inflammatory infiltration was present, and mucus-secreting cells appeared slightly reduced, suggesting early impairment of mucosal protection (Figure 2).

A B

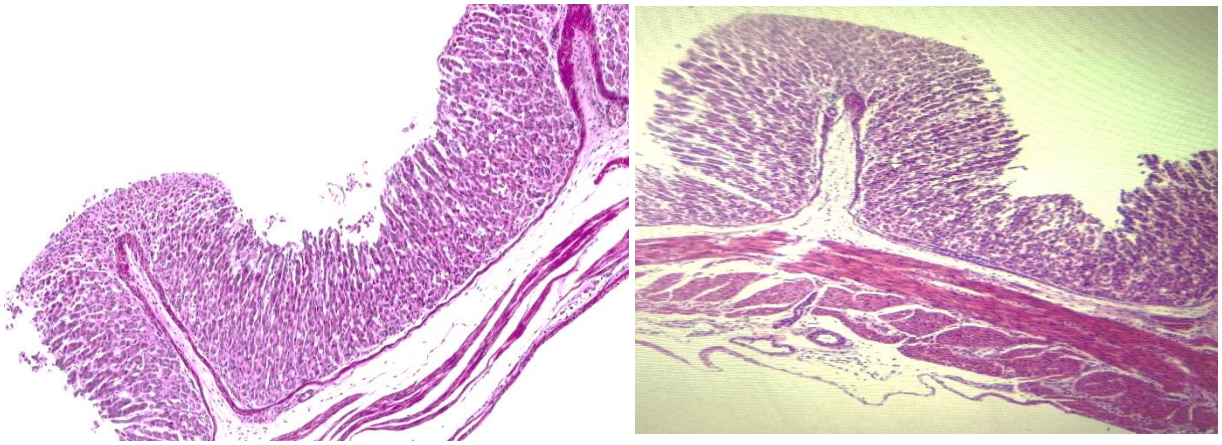

Figure 2. Histological section of a stomach from a hamster, intraperitoneal injection of 100mg/kg. Cyclophosphamide. Stain H & E (A X40) and PAS (B X40)

At 200 mg/kg, marked histopathological alterations were evident. The mucosal layer showed extensive disruption, including epithelial rupture, abnormal cell death, and distortion of gastric pits. The lamina propria exhibited loss of normal cellular architecture. Submucosal changes indicated abnormal cellular responses, though overt inflammation was limited. The muscularis externa demonstrated mild to moderate degeneration of smooth muscle fibers. PAS staining revealed a pronounced reduction in mucopolysaccharide content, reflecting loss of functional mucus-secreting cells and impaired protective capacity of the gastric mucosa (Figure 3).

Overall, the histological results demonstrate a clear dose-dependent gastric toxicity profile for cyclophosphamide. While low doses (100 mg/kg) produced only mild and reversible changes, high doses (200 mg/kg) resulted in severe mucosal injury, structural disruption, and diminished mucus secretion. The correlation between PAS staining and epithelial damage highlights impaired mucosal protection as a key mechanism underlying cyclophosphamide-induced gastric toxicity.

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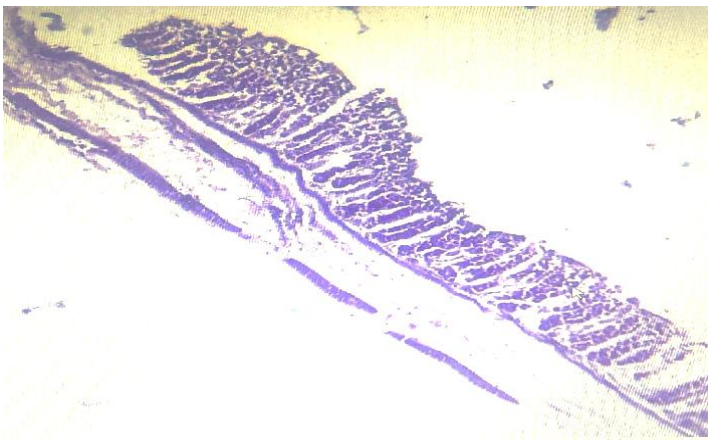

Figure 3. Histological section of a stomach from a hamster, which was intraperitoneal injection of 200 mg/kg cyclophosphamide. Stain H & E X40

Discussion

The present study demonstrates that cyclophosphamide induces dose-dependent histopathological alterations in the gastric mucosa of golden hamsters. At lower doses (100 mg/kg), the gastric architecture remained largely intact, with only mild epithelial erosion and minimal inflammatory infiltration. In contrast, higher doses (200 mg/kg) produced severe mucosal disruption, epithelial rupture, loss of gastric pits, and reduced mucopolysaccharide secretion, indicating impaired mucosal protection. These findings confirm that cyclophosphamide exerts progressive gastric toxicity, consistent with its known systemic adverse effects. Previous studies have documented cyclophosphamide-induced toxicities in the liver and kidneys, characterized by necrosis, inflammation, and architectural distortion [3,10]. However, the stomach has received comparatively less attention.

Our results extend current knowledge by providing detailed histological evidence of gastric injury, highlighting the stomach's vulnerability as a primary site exposed to circulating cytotoxic metabolites. The observed reduction in PAS-positive mucopolysaccharides at higher doses suggests that loss of mucus-secreting cells may be a key mechanism underlying gastric injury, predisposing the tissue to ulceration and impaired barrier function. The findings align with reports of chemotherapy-induced gastrointestinal complications, including mucositis, ulceration, and impaired nutrient absorption [8,14]. Importantly, the dose-dependent nature of the damage emphasizes the need for careful monitoring of gastric function during cyclophosphamide therapy**,** particularly at higher doses.

The golden hamster model proved suitable for assessing gastric toxicity, offering reproducible histological features that can be extrapolated to human pathology [3,10]. From a clinical perspective, these results underscore the importance of integrating histological monitoring and protective strategies into treatment protocols. Agents that preserve mucosal integrity, such as cytoprotective drugs or dietary interventions, may mitigate gastric injury. Furthermore, the findings highlight the potential of using preclinical models to optimize dosing regimens and reduce gastrointestinal complications in patients undergoing cyclophosphamide therapy.

This study was limited by its short duration and focus on acute toxicity. Chronic exposure studies are needed to evaluate long-term gastric effects. Additionally, molecular analyses of apoptosis, oxidative stress, and inflammatory pathways would provide mechanistic insights into cyclophosphamide-induced gastric injury. Future research should also explore protective interventions to counteract mucosal damage.

Conclusion

This study demonstrates that cyclophosphamide induces dose-dependent histopathological alterations in the gastric mucosa of golden hamsters. At lower doses (100 mg/kg), the gastric architecture remained largely intact, with only mild epithelial changes, whereas higher doses (200 mg/kg) produced severe mucosal disruption, epithelial rupture, and diminished mucopolysaccharide secretion. These findings highlight impaired mucosal protection as a key mechanism of gastric toxicity. The results underscore the importance of histological monitoring during cyclophosphamide therapy, particularly at higher doses, to prevent gastrointestinal complications. The golden hamster model proved to be a relevant and reproducible preclinical system for evaluating chemotherapy-induced gastric injury. Future studies should extend these observations by exploring chronic exposure models, molecular mechanisms of toxicity, and potential protective interventions. Such research will contribute to optimizing cyclophosphamide dosing regimens and improving patient outcomes in clinical oncology.

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Ethical approval
Ethical approval for this study was granted by the Animal Ethics Committee of the University of Benghazi. All procedures complied with institutional and international guidelines for the care and use of laboratory animals.

Conflict of Interest
The authors declare that they have no conflicts of interest related to this study.

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- Manuscript Drafting & Revision: Abeer Hussien Amer, Maysoon Faraj Elrashdy, Rima Ahmed Benomran. All authors read and approved the final manuscript.

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