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Nephrotoxicity Induced by Cytosar in Rabbits Kidneys (A Histological Study)

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Abstract The current study was carried out to assess the nephrotoxicity induced by Cytosar in kidneys of rabbits from the histological aspect. The treated group with a dose of (50 mg/kg/daily) of Cytosar for 5 days, showed clear histological changes represented by glomerular atrophy and widening of Bowman's spaces, infiltration of lymphocytes and macrophages within cortex, renal tubular necrosis, cortical hemorrhage and fibrosis as well as formation of tubular hyaline cast was also observed. The present study showed that Cytosar is a nephrotoxic drug when used repeatedly at this dosage which could lead to irreversible renal damage and finally renal failure.

Keywords: *Cytosar, nephrotoxicity, rabbits kidneys*

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1. Introduction

Cytosar is an efficient treatment of leukemia [1] it inhibits DNA polymerase of cancer cells causing the death of these cells. Cytosar structure joins the cytosine base with arabinose sugar, hence it also named "Cytosine-Arabinose" [2].

Cytosar has a similar structure almost to that of human {cytosine deoxyribose} to be integrated within human DNA, but different enough to destroy the cancer cells, for this reason, this mechanism is responsible of termination of malignant cells [3].

The nephrotoxicity is one of the most common types of renal diseases that may occur as a sequel of chemotherapy [4].

The purpose of this research is to reveal the structural changes induced by Cytosar on rabbits kidneys histology.

2. Materials and Methods

The study was carried out on 12 rabbits (mixed, male & female) with a weight of 1.25-1.5 kg and aged 4 months. The animals were divided into 2 groups and each experimental group is formed of (6 rabbits) which was given the following:

Group A: received intraperitoneal injection of 1 ml of normal saline one time daily for 5 days to represent the control group.

Group B: received intraperitoneal injection of **(50 mg/kg/day)** of Cytosar for 5 days and served as treated group [5]. This dosage is calculated according to the mentioned study in reference [5] that used a dosage of {**1000 mg of Cytosar per square meter}** in human, and by conversion of this dosage from **(Body Surface Area Based Dosing)** to **(per kilogram Based Dosing)** using the Medscape equation (reference.medscape.com/calculator/bsa-dosing), we would find that dosage of **(50 mg/kg/day)** which means (**75 mg)** for each single rabbit, will mathematically equal to that of **(1000 mg per square meter in human)**, in case of the body weight of each rabbit was 1.5 kg & the height of animal was 20 cm.

Then rabbits of the 2 groups were sacrificed under light ether anesthesia after 5 days.

Then kidneys of every animal were prepared for histological study by placing them in 10% formalin solution for 24 hours to complete the fixation step, then each specimen was immersed in a successive concentrations of alcohol {35% to 100%} for a period of {5 minutes}. After that, the samples of each tissue were placed in two changes of xylene to be cleared before its embedding in paraffin for sectioning. finally each paraffin block was sectioned to thickness of "5 µm" and stained with "hematoxylin and eosin" to examine for the histological changes under light microscope.

3. Results & Observations

Histological architecture of the sections in the control group {Group A} showed normal morphology of the kidney tissues {Figure 1}.

The histological sections of the treated group with Cytosar {Group B} showed glomerular atrophy and widening of Bowman's spaces {Figure 2}, infiltration of lymphocytes within cortex {Figure 3, Figure 4, Figure 5}, renal tubular necrosis and sloughing of the epithelial cells lining the renal tubules {Figure 3}, formation of tubular hyaline casts {Figure 4} as well as cortical hemorrhage and interstitial fibrosis were also noticed {Figure 5}.

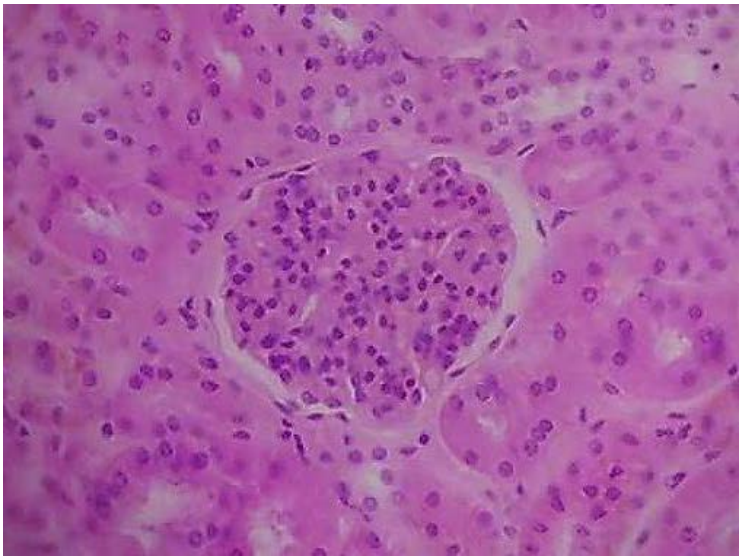

Figure 1. Histological slide of kidney tissue from {group A} showed normal architecture of the renal tissue constitution. H & E, 400x

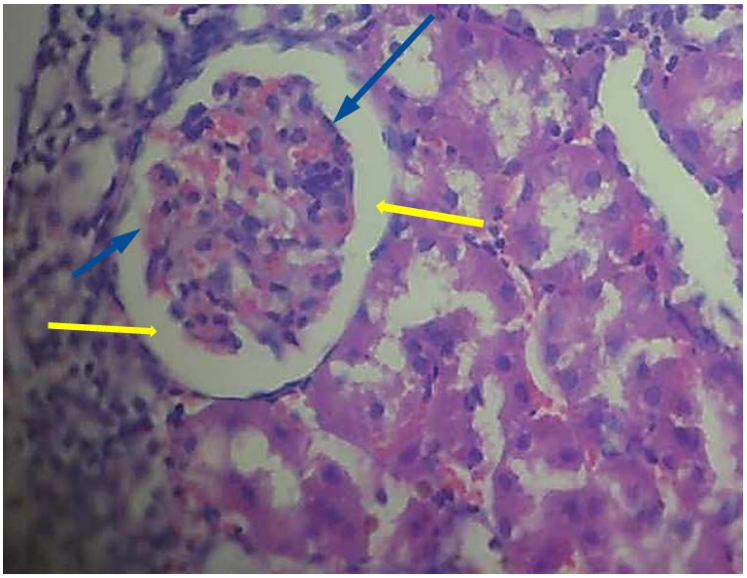

Figure 2. Histological slide of kidney tissue from {group B} revealed glomerular tuft atrophy {blue-arrows} and urinary space widening {yellow-arrows}. H & E, 400x

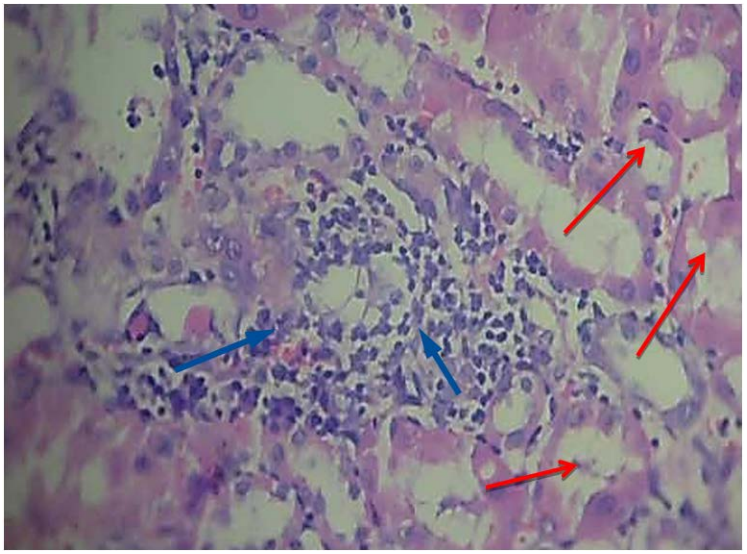

Figure 3. Histological slide of kidney tissue from {group B} revealed infiltration of lymphocytes within cortex (blue-arrows), necrosis of renal tubules and sloughing of the renal tubular epithelial cells {red-arrows}. H & E, 400x

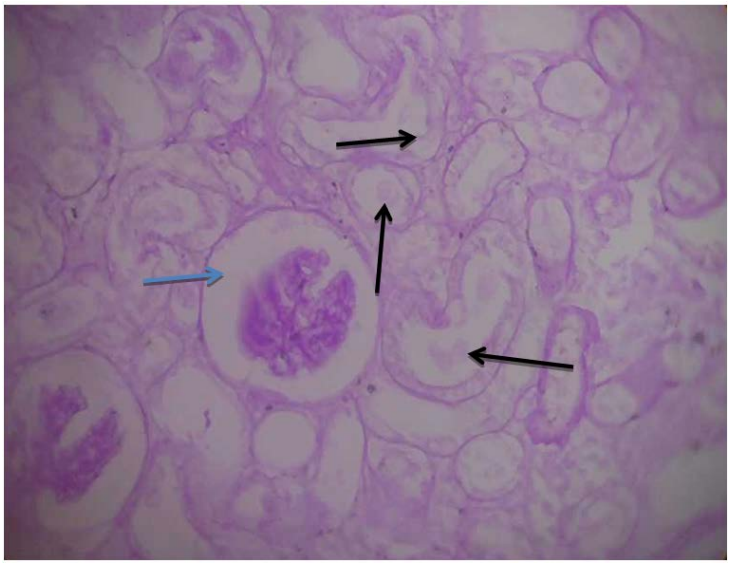

Figure 4. Histological slide of kidney tissue from {group B} revealed necrosis of renal tubules and sloughing of the renal tubular epithelial cells {black-arrows} and urinary space widening {blue-arrow}. PAS, 400x

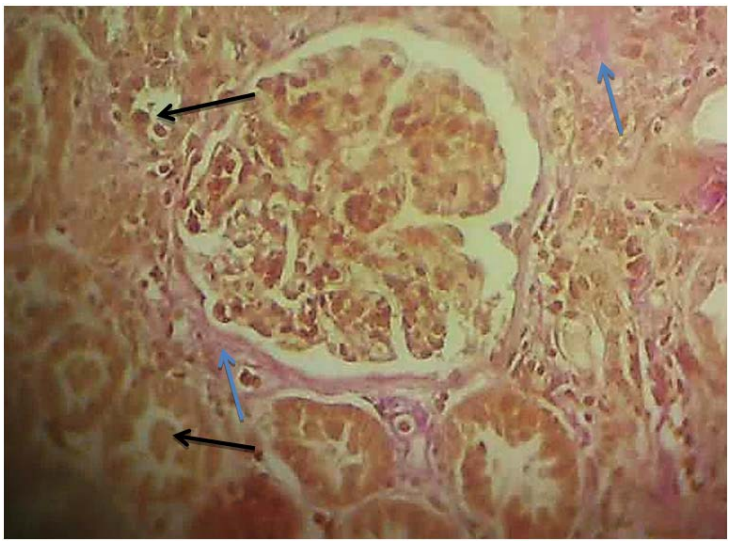

Figure 5. Histological slide of kidney tissue from {group B} revealed necrosis of renal tubules and sloughing of the renal tubular epithelial cells {black-arrows} in addition to interstitial fibrosis {blue-arrow}. Orcin-Vangieson, 600x

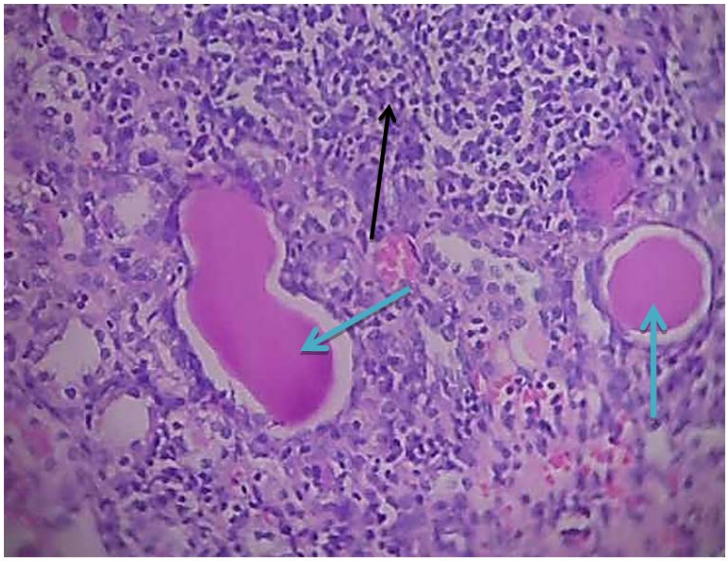

Figure 6. Histological slide of kidney tissue from {group B} revealed infiltration of mononuclear inflammatory cells {black-arrow} & formation of hyaline cast inside many tubular lumens {blue arrows}. H &E, 400x

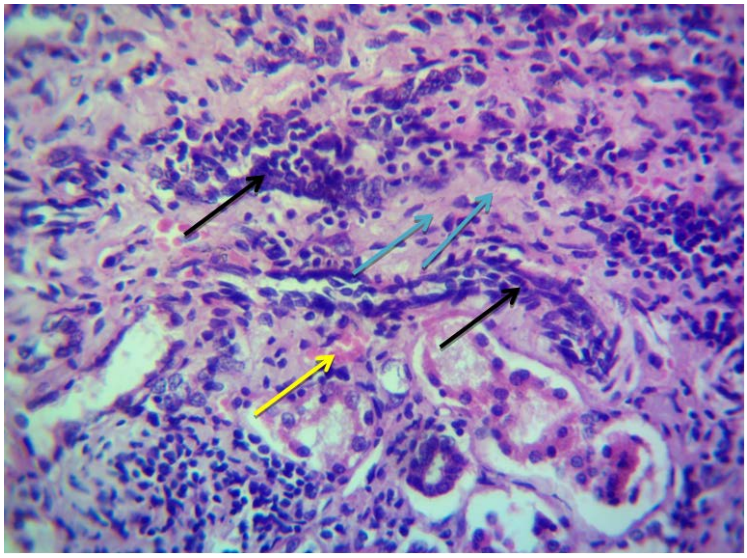

Figure 7. Histological slide of kidney tissue from {group B} revealed infiltration of mononuclear inflammatory cells {black-arrows}, cortical hemorrhage {yellow-arrow} and interstitial fibrosis {blue-arrows}. H & E, 400x

4. Discussion

Cytotoxic agents which are used for treatment of tumors may lead to various histological changes in kidneys, as this organ is the main organ that is responsible of excretion and metabolism of those toxic substances [6]. Cytotoxic drugs may influence glomerulus, renal tubular cells and interstitium, with many clinical signs which could extend from serum creatinine elevation to acute renal tissue injury [7,8].

The current experiment is possibly the **first experimental research** that focuses on Cytosar nephrotoxicity from the histological aspect, as most of the previous studies on Cytosar were concentrating on biochemical & blood parameters as well as clinical manifestations but not renal histological changes.

Nephrotoxicity seen in the 2nd group **{group B}** is demonstrated by several histological changes, like glomerular atrophy and widening of Bowman's spaces, infiltration of lymphocytes within cortex, renal tubular necrosis and sloughing of the epithelial cells lining the renal tubules, formation of tubular hyaline casts as well as cortical hemorrhage and interstitial fibrosis were also seen.

Widening of the urinary spaces and glomerular atrophy may be occurred due to the increased concentration of drug in the blood which leads to constriction of the glomerular capillaries resulting in lowering of the drug filtration inside the glomeruli and finally increase the drug adverse effects which in turn can finally leads to urinary spaces widening and atrophy of the glomerular tufts [9].

Anticancer drugs excretion through the kidneys needs peritubular transport of these drugs to allow entrance to the epithelial surface of the renal tubules [10]. Later when these drugs reach basolateral membrane, they are transported via organic cation and anion transporters into the cells, then excreted by efflux transporters on the apical membrane into tubular lumens [11]. Any inhibition or dysfunction of the kidney efflux transporters can leads to accumulation of the drug inside the cells of renal tubules which in turn leads to drug nephrotoxicity represented by sloughing of the epithelial cells lining the renal tubules and necrosis of the renal tubular cells [12].

Kidney is the organ that responsible of drugs oxidation into different metabolites through a specific enzymatic system situated inside the renal parenchyma. Kidney tissues could be damaged by a number of these metabolites by several ways, like "oxidative stress" production and generation of "reactive oxygen species" [13]. The Cytosar generated (reactive oxygen species) trigger a continuous renal inflammatory response which support mononuclear inflammatory cells infiltration [14]. These inflammatory cells are responsible of the fibrosis that occurred in renal interstitium via production of fibro-genic agents which intermediate the stimulation of myofibroblasts to generate extracellular matrix [15].

From another side, the oxidative Stress (OS) could affect the nephrotic hemodynamics, because it either raises the vascular resistance or reduce the renal blood flow that finally lead to blood pressure rising which is hard to control leading to rapture of renal capillaries and bleeding [16,17].

The formation of hyaline cast may be due to the reduction of tubular protein reabsorption, leading to aggregation of those proteins inside tubular lumens to form the hyaline casts [18].

The mentioned results of the study suggested that Cytosar is a nephrotoxic drug when used alone, hence more researches are needed on Cytosar to find the level of nephrotoxicity occurred at different doses and at different time periods.

References

[1] Momparler, R.L., "Optimization of cytarabine (ARA-C) therapy for acute myeloid leukemia," *Exp Hematol Oncol*, 6 (2). 20. 2013.

[2] Rechkoblit, O., Choudhury, J.R., Buku, A., Prakash, L., Prakash, S. and Aggarwal, A.K., "Structural basis for polymerase η-promoted resistance to the anticancer nucleoside analog Cytarabine," *Sci Rep*, 8 (1). 12702. Aug. 2018.

[3] Konda, N., Prashanth, P., Arvind, G. and Shah S., "Pharmaceutical development and compatibility studies on Cytarabine injection," *Asian J. Pharm. Clin. Res*, 3 (6). 142-145. 2013.

[4] Norbert, L., "Nephrotoxicity of recent anti-cancer agents," *Clin Kidney J*, 7 (1). 11-22. 2014.

[5] Löwenberg, B., Pabst, T., Vellenga, E., et al., "Cytarabine dose for acute myeloid leukemia," *N Engl J Med*, 364 (11). 1027-1036. 2011.

[6] Perazella, M.A., "Onco-Nephrology: Renal Toxicities of Chemotherapeutic Agents," *Clin J Am Soc Nephrol*, 7 (10). 1713-1721. 2012.

[7] Morrissey, K.M., Stocker, S.L., Wittwer, M.B., Xu, L. and Giacomini, K.M., "Renal transporters in drug development," *Annu Rev Pharmacol Toxicol*, 53. 503-529. 2013.

[8] Malyszko, J., Kozlowska, K., Kozlowski, L. and Malyszko, J., "Nephrotoxicity of anticancer treatment," *Nephrol Dial Transplant*, 32 (6). 924-936. 2017.

[9] Pazhayattil, G.S. and Shirali, A.C., "Drug-induced impairment of renal function," *Int J Nephrol Renovasc Dis*, 7. 457-468. 2014.

[10] Izzedine, H. and Perazella, M.A., "Anticancer Drug-Induced Acute Kidney Injury," *Kidney Int Rep*, 2 (4). 504-514. 2017.

[11] Rodríguez-Iturbe, B., Vaziri, N.D., Herrera-Acosta, J. and Johnson, R.J., "Oxidative stress, renal infiltration of immune cells, and salt-sensitive hypertension: all for one and one for all," *Am J Physiol Renal Physiol.* 286 (4). 606-616. 2004.

[12] Miller, R.P., Tadagavadi, R.K., Ramesh, G. and Reeves, W.B., "Mechanisms of Cisplatin nephrotoxicity," *Toxins (Basel)*, 2 (11). 2490-2518. 2010.

[13] Al-Jammas, S. and Al-Hubaity, A.Y., "The Effects of Vitamin C on the Structure of Wistar Albino Rat's kidney," *Medical Journal of Tikrit*, 2 (172). 116-119. 2011.

[14] Choi. Y.M., Kim, H.K., Shim, W., et al., "Mechanism of Cisplatin-Induced Cytotoxicity Is Correlated to Impaired Metabolism Due to Mitochondrial ROS Generation," *PLoS One*, 10 (8). e0135083. 2015.

[15] Liu, Y., "Cellular and molecular mechanisms of renal fibrosis," *Nat Rev Nephrol*, 7 (12). 684-696. 2011.

[16] Abdelhalim, M. and Jarrar, B.M., "The appearance of renal cells cytoplasmic degeneration and nuclear destruction might be an indication of GNPs toxicity," *Lipids in Health and Disease*, 10. 147. 2011.

[17] Lawenda, B.D., Kelly, K.M., Ladas, E.J., Sagar, S.M., Vickers, A. and Blumber, J.B., "Should Supplemental Antioxidant Administration Be Avoided During Chemotherapy and Radiation Therapy?," *J Natl Cancer Ins*, 100. 773-783. 2008.

[18] Hutchison, C.A., "Batuman V, Behrens J, et al. The pathogenesis and diagnosis of acute kidney injury in multiple myeloma," *Nat Rev Nephrol*, 8 (1). 43-51. 2011.