Hematological alterations in erythrogram, leukogram, and thrombogram of rats with doxorubicin-induced renal toxicity

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Abstract
Doxorubicin (DOX) is a widely used antineoplastic agent in cancer treatment; however, it has several drawbacks that can cause harmful effects on various organs, especially the kidneys. Nevertheless, it does not fully reveal the extent of DOX-induced tissue damage. Therefore, it is crucial to clarify the risks associated with DOX-mediated tissue injury. A total of 14 female Wistar Albino rats were divided into two equal groups: Control and Dox. The Dox group received a single dose of 20 mg/kg DOX. Kidney, liver, and blood samples were collected for further analysis. Hematoxylin-Eosin staining and biochemical tests were conducted to assess DOX-induced tissue damage. Our results showed that the Dox group experienced significant glomerular atrophy. Parameters such as RBC, HGB, HCT, and MCHC were also significantly higher compared to the Control group. No significant differences were observed in liver tissues between the groups. Inflammatory markers were also evaluated. NLR and SII scores showed statistically significant differences between the groups. Administration of DOX caused alterations in erythrocyte and leukocyte parameters, with notable changes in renal tissue characterized by glomerular atrophy.

Keywords: *Doxorubicin, adverse effect, drug toxicity, acute renal injury*

INTRODUCTION

Cancer is known as one of the deadliest diseases worldwide, with a rapidly rising mortality rate. Various chemotherapeutic drugs are used to fight cancer, each differing in its mechanisms of action and chemical structure (İyi Altınışık, & İşler., 2024). Doxorubicin (DOX), a commonly used chemotherapy drug in clinical settings, is a hydrophilic compound that appears more reddish at neutral pH and is sensitive to light. It is derived from Streptomyces peucetius var. caesius. DOX has been used for over forty years to treat multiple cancers, such as the lung, breast, thyroid, and ovary. As part of the anthracycline antibiotic group, DOX works through three main mechanisms: (i) inducing DNA damage, (ii) activating the DNA damage response (DDR), and (iii) triggering apoptosis or cell cycle arrest. The recommended total dose of DOX should not exceed 450–500 mg/m², because higher doses significantly increase the risk of side effects (Kciuk et al., 2023; Prasanna et al., 2020; Pugazhendhi et al., 2018; Sritharan & Sivalingam, 2021).

Recent studies have increasingly emphasized that doxorubicin-induced renal and hepatic toxicity is mediated through complex interactions involving oxidative stress, mitochondrial dysfunction, iron-dependent lipid peroxidation, and inflammatory signaling. Despite extensive research, the precise hematological signatures that precede or accompany renal structural injury remain poorly defined. Integrating current evidence, particularly reports indicating early erythrocyte and leukocyte perturbations as sensitive biomarkers, strengthens the rationale for investigating hematological–renal interactions. This study therefore expands existing literature by offering a focused evaluation of DOX-induced hematological alterations in parallel with histological assessment, providing a more comprehensive depiction of renal susceptibility and systemic inflammatory burden.

Although DOX is considered a promising therapeutic agent for a wide range of tumours species, it is associated with several adverse effects (Sritharan & Sivalingam, 2021). One of the major concerns with DOX administration is its toxicity to the hepatorenal system. Recent research indicated that while the incidence of renal damage is approximately 4.5%, nearly 40% of patients receiving DOX developed liver injury. Moreover, the toxicity mechanism in both tissues is not fully understood, and there is limited information about the effects (Botros et al., 2024; Chen et al., 2016). DOX had detrimental effects on liver cells by triggering oxidative stress response through excessive release of radicals in hepatic cells. Also, DNA is damaged due to decreased glutathione (GSH) level. To manage the condition, DOX, which is a localised intracellular area, is removed through the ATP-dependent ABC proteins (P-glycoprotein) in the liver. It causes the consumption of ATP, so the regeneration capacity is decreased (Ajaykumar & Ajaykumar, 2020). DOX has a comparable effect on the renal system. DOX consists of plenty of free radicals. It results in nephrotoxicity, that raises creatinine (Cr) and blood urea nitrogen (BUN) levels and indicates renal cell destruc-

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tion. Additionally, DOX leads to nephropathy through interfering with the kidney's glandular podocytes (Ajaykumar & Ajaykumar, 2020; Renu et al., 2022).

The goal of the investigation was to determine the effects of DOX-induced hepatorenal toxicity by monitoring the hematological profile of experimental animals and identifying any potential changes in the renal system that may occur.

MATERIAL AND METHODS

Animals

The present study included eighteen Wistar Albino female rats (G power: n≥6) purchased from Kafkas University Experimental Research Application and Research Centre. Rats were housed individually at standard humidity (45%–50%) and temperature (22±2°C), with a 12-h dark/light cycle and fed *ad libitum*.

Groups

A total of 14 rats that were 2-3 months old and their an average weight of 200-250 g were divided into two groups based on their average weight, as listed below.

Control Group (n=7): The group with no administration

Dox Group (n=7): The group of DOX administration

Doxorubicin Administration

The cumulative dose of DOX was preferred according to previous literature (Kaymak et al., 2021). A single dose of DOX (Saba Pharmaceuticals) was applied intraperitoneally at a dose of 20 mg/kg (Yagmurca et al., 2015).

Sacrification and Specimen Collecting

All animals went under general anesthesia via ketamine hydrochloride and xylazine (75-15 mg/kg). The blood samples were collected by cardiac puncture. Then, the blood samples were stored at +4 °C for hematological assessment. For histological examination, both liver and kidney were taken in 10% neutral buffered formalin before tissues were gathered.

Histopathological Assessment

The tissues were then fixed for 48 hours, and then the routine tissue processing protocol was performed. Tissues were embedded in paraffin, and then 4-5 µ sections were taken from paraffin blocks. Tissue sections were prepared and stained with Hematoxylin & Eosin (H&E) for histological examination (Sozmen et al., 2005). The stained sections were evaluated under a light microscope (Olympus BX 53, Japan, Tokyo).

Hematological Assessment

The blood samples were analysed using a hematological analyzer for hematological evaluation. Different tested hematological parameters are given in Table 1. Utilise the values Neutrophil-to-lymphocyte ratio (NLR), Lymphocyte-to-monocyte ratio (LMR), Platelet-to-lymphocyte ratio (PLR), Systemic immune-inflammation index (SII calculated as platelet × neutrophil/lymphocyte), and Systemic inflammation response index (SIRI calculated as monocyte × neutrophil/lymphocyte) were calculated using the formula.

Statistical Analysis

All analyses were performed using SPSS v27.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used for evaluating the normality, and Levene's test was preferred for assessing the homogeneity of variances was assessment. Differences between groups were analyzed using the Independent Samples t-test. Results were given as mean ± standard error (Mean ± SE), and a significance level of $p < 0.05$ was considered statistically significant.

RESULTS

Histopathological Results

The liver and kidney tissues were evaluated after H-E staining. According to the evaluation, the kidney tissue sections of the Dox group have glomerular atrophy (Figure 1C). However, the hepatological structure of the Dox group was the usual (Figure 1A). Moreover, both liver and kidney tissues of the control groups have regular histological structure (Figure 1B and 1D).

Table 1. *Hematological parameters*

ALY#: Absolute atypical lymphocyte count	**LYM#**: Absolute lymphocyte count
ALY%: Atypical lymphocyte percentage	**LYM%**: Lymphocyte percentage
BAS#: Absolute basophil count	**MCH**: Mean corpuscular hemoglobin
BAS%: Basophil percentage	**MCHC**: Mean corpuscular hemoglobin concentration
EOS#: Absolute eosinophil count	**MCV**: Mean corpuscular volume
EOS%: Eosinophil percentage	**MON#**: Absolute monocyte count
HCT: Hematocrit	**MON%**: Monocyte percentage
HGB: Hemoglobin	**MPV**: Mean platelet volume
IMG#: Absolute immature granulocyte count	**NEU#**: Absolute neutrophil count
IMG%: Immature granulocyte percentage	**NEU%**: Neutrophil percentage
IML#: Absolute immature lymphocyte count	**PCT**: Plateletcrit.
IML%: Immature lymphocyte percentage	**PLT**: Platelet count
IMM#: Absolute immature monocyte count	**RBC**: Red blood cell count
IMM%: Immature monocyte percentage	**RDW**: Red cell distribution width
LIC#: Absolute large immature cell count	**WBC**: White blood cell count
LIC%: Large immature cell percentage	

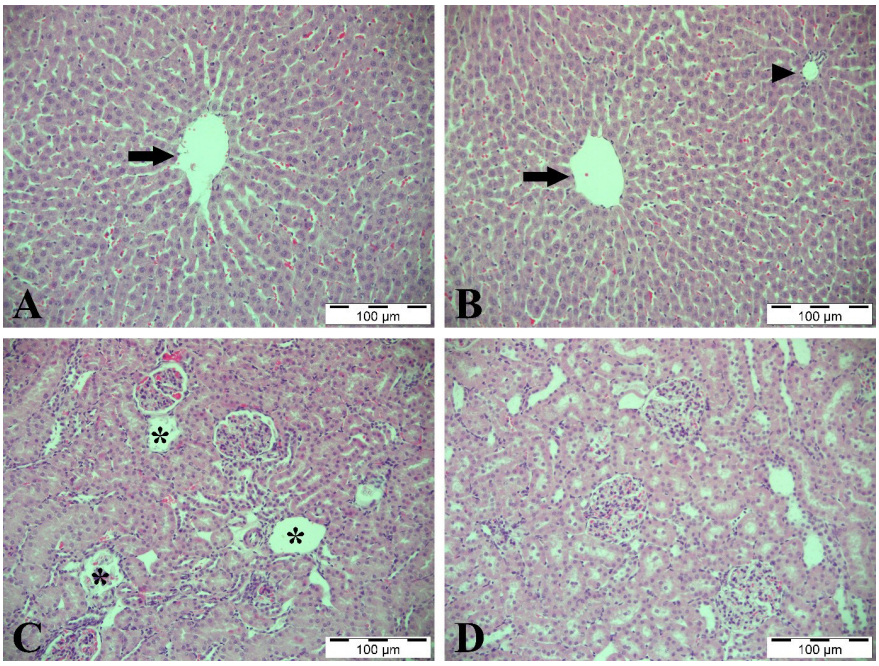

Figure 1. *The H&E-stained liver and kidney sections. A: Dox and B: Control groups of liver tissue (Arrow: vena centralis, Triangle: Portal triad). C: Dox A and D: Control groups of liver tissue (*: Glomeruler atrophy).*

Hematological Results

The DOX-mediated hematological alteration is evaluated in four main areas. The erythrocyte results indicated that RBC, HGB, HCT, and MCHC values increased statistically in the Dox group (p values, respectively, p = 0.006, p = 0.003, p = 0.005, and p = 0.024). On the other hand, there was no statistically significant difference in MCV, MCH, and RDW levels compared to the Control group (p>0.05, Table 2).

Table 2. *Comparison of groups in terms of erythrogram markers (* p<0.05).*

	CONT	DOX	P value
RBC (10^{12}/l)	6.8±0.25	7.87±0.17	p=0.006*
HGB (g/dl)	14.12±0.51	16.28±0.25	p=0.003*
HCT (%)	39.72±1.29	44.77±0.5	p=0.005*
MCV (fL)	58.5±0.56	57±0.77	p=0.148
MCH (pg)	20.75±0.22	20.75±0.33	p=1.000
MCHC (g/dl)	35.45±0.2	36.47±0.33	p=0.024*
RDW (fl)	12.58±0.59	12.07±0.32	p=0.460

The second area was leukogram parameters. LYM%, NEU%, LIC%, and NEU# were elevated in the Dox group compared to the Control group (p values p=0.012, p=0.013, p=0.044, and p=0.033, respectively). In contrast to the alteration, other evaluated parameters showed no differences between the two groups (p > 0.05, Table 3).

Platelet markers were another group of examined values. There were no statistically significant differences between the Control and Dox groups (p > 0.05, Table 4).

Lastly, inflammatory parameters were evaluated. NLR and SII scores were statistically different between the groups (p=0.013 and p=0.016, Table 5).

Table 3. *Leukogram parameters compared between groups (* p<0.05).*

	CONT	DOX	P value
WBC (×10^3/µL)	13.53±2.64	8.59±2.71	p=0.221
LYM% (%)	93.1±1.45	81.9±3.36	p=0.012*
MON% (%)	0.87±0.13	1.12±0.17	p=0.264
NEU% (%)	5.63±1.28	15.93±3.16	p=0.013*
EOS% (%)	0.22±0.12	0.92±0.31	p=0.059
BAS% (%)	0.18±0.07	0.13±0.06	p=0.604
ALY% (%)	1.93±0.14	1.03±0.28	p=0.016
LIC% (%)	0.33±0.16	0.83±0.15	p=0.044*
IML% (%)	0.07±0.03	0.13±0.03	p=0.188
IMM% (%)	0±0	0.05±0.02	p=0.076
IMG% (%)	0.22±0.16	0.65±0.13	p=0.063
LYM# (×10^3/µL)	12.72±2.62	7.42±2.73	p=0.191
MON# (×10^3/µL)	0.12±0.03	0.1±0.03	p=0.593
NEU# (×10^3/µL)	0.63±0.07	1±0.13	p=0.033*
EOS# (×10^3/µL)	0.02±0.01	0.06±0.02	p=0.051
BAS# (×10^3/µL)	0.03±0.01	0.01±0	p=0.291
ALY# (×10^3/µL)	0.27±0.07	0.13±0.08	p=0.190
LIC# (×10^3/µL)	0.03±0.01	0.06±0.01	p=0.072
IML# (×10^3/µL)	0.01±0	0.01±0	p=1.000
IMM# (×10^3/µL)	0±0	0.01±0	p=0.049
IMG# (×10^3/µL)	0.02±0.01	0.04±0.01	p=0.167

Table 4. *Comparison of groups in terms of platelet markers.*

	CONT	DOX	P value
PLT (×10^3/µL)	536.67±42.2	412.5±37.62	p=0.053
MPV (fL)	6.8±0.12	7.47±0.52	p=0.263
PCT (%)	0.36±0.03	0.3±0.02	p=0.128

Table 5. *Inflammatory ratios and index between the groups (* p<0.05).*

	CONT	DOX	P value
NLR	0.06±0.02	0.2±0.04	p=0.013*
PLR	49.6±9.66	77.93±14.42	p=0.133
MLR	0.01±0	0.01±0	p=0.115
SII score	31.79±7.85	77.61±13.68	p=0.016*
SIRI score	0.01±0	0.02±0	p=0.076

DISCUSSION

This study mainly aimed to evaluate the effects of DOX-induced renal toxicity on hematological parameters. The major finding is that renal toxicity affects several erythrocyte, leukogram, and inflammatory values. It was determined that erythrocytes, monocytes, and leucocytes were higher in the Dox group than in the Control group. In addition, a number of biomarkers related to the cells have been altered. Moreover, although renal toxicity was observed, the liver tissues surprisingly showed a regular structure. DOX-related hepatotoxicity is thought to be more common than renal impairment, according to research (Botros et al., 2024). Diverse metabolic rates among species, gender disparities, or variations in dosage and time of administration may have constrained the response.

DOX has been shown to cause renal toxicity resulting in acute kidney injury (AKI), which can disrupt kidney function that could result in mortality. In kidney tissue, glomerular atrophy is accepted as a signal of AKI (Kim et al., 2017; Yagmurca et al., 2015; Zeng et al., 2020). In addition, in the study, glomerular atrophy was examined for renal toxicity. It is shown that the kidney tissues of the Dox group have prominent glomerular atrophy. On the other hand, histopathological investigation of liver tissue showed no influence of DOX exposure.

Kidneys are a multifunctional organ, releases Erythropoietin (EPO), so they can lead the production of erythrocytes (Bayır et al., 2023). The study it is found that RBC, HGB, HCT, and MCHC parameters are altered via DOX. The condition could be related to EPO production, as it was presented that causes renal stress (Bayır et al., 2023). Moreover, another result is that the amount of RBC enhancement supports the idea.

Previous studies indicated that acute DOX toxicity modified P450 expression had a pivotal role in arachidonic acid metabolism; moreover, the cyclooxygenase and the lipoxygenase pathways in several tissues (Zordoky et al., 2010, 2011; Zordoky & El-Kadi, 2008). The situation is attributed to the reason of the DOX-related inflammation (Zordoky et al., 2011). Our findings show that some inflammatory scores, that NLR and SII, were elevated in the Dox group. Additionally, a significant increase in leukocyte subgroups, especially in NEU% and NEU# values, is presented. Therefore, determined that the results could be related to P450 enzyme activity.

Interestingly, no significant differences were detected in platelet parameters between the groups. This may be explained by two factors. First, the lifespan of platelets in rats is approximately 4–5 days; thus, despite potential suppression of megakaryopoiesis, circulating platelets may not have yet decreased to a detectable level at the time of sampling. Second, DOX exhibits tissue- and cell-specific toxicity, with more pronounced effects on renal glomeruli and erythroid and leukocytic series, whereas its direct impact on platelets appears to be limited under the present experimental conditions (Afsar et al., 2020).

The observed hematological alterations align with recent mechanistic studies showing that DOX triggers redox imbalance, inflammatory cytokine release, and bone marrow stress, all of which can contribute to variations in erythrocyte and leukocyte indices. The increase in neutrophil-related parameters parallels reports linking DOX exposure to NF-κB activation and enhanced myeloid-cell mobilization. Additionally, the preservation of platelet indices in this study supports the notion that thrombopoiesis may be less immediately affected than erythropoiesis or leukopoiesis under acute renal toxicity. These findings collectively emphasize that hematological markers, particularly NLR and SII, may function as early indicators of tissue-specific toxicity. The discussion is further strengthened by contextualizing the results within DOX-responsive pathways, supporting a clearer interpretation of renal vulnerability and systemic inflammatory signaling.

This study contains several limitations. Firstly, only female rats were used in the study so hormonal alteration could affect protection against the toxicity. Secondly, due to the small sample size is a lack of the study. Moreover, histopathological and biochemical results are limited to explaining the underly mechanism, so further studies are required to determine certain reasons.

In conclusion, DOX administration induced alterations in erythrocyte and leukocyte parameters, while causing excessive toxicity in renal tissue characterized by glomerular atrophy. The significant changes in hematological parameters may serve as potential biomarkers for assessing inflammation and immune response. Future studies should be established to elucidate dose-dependent and duration procedures, in addition to the evaluation of oxidative stress markers, cytokine levels, and immunohistochemical assays.

Ethical approval

Ethical approval from Kafkas University Animal Experiments Local Ethics Committee (number: 2025/139, date: 07.03.2025).

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Contribution disclosures

HAE, MM, and MOC designed the study. MM and TG performed experimental procedures. HN performed histopathological analysis. CA calculated indices and performed statistical analysis. HAE, CA, and MAO participated in drafting and revising the manuscript. The published version of the manuscript has been read and approved by all authors.

Availability of data and materials

The data and materials of this study are available from

the corresponding author upon reasonable request.

Conflict of interests

The authors declared that there is no conflict of interest.

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