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Morphological changes in blood cells in a rat model of cadmium poisoning

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Abstract

Aim: Cadmium (Cd), a toxic metal that accumulates in the environment as a result of industrial and agricultural activities, poses a serious threat to the health of living organisms. Cd is also an important component of environmental pollution. Cd salts dissolve in organs. Therefore, it is one of the heavy metals that can cause toxic effects on the hematological system. The aim of this study was to investigate the morphological changes in blood cells induced by cadmium (Cd) exposure in a rat model.

Methods: Fourteen male Wistar Albino rats (8-10 weeks old; 300-350 g) were divided into control and Cd-exposed groups, each consisting of seven rats. Cadmium chloride was administered via intraperitoneal injection. Peripheral blood smear analysis was performed to assess the morphology of blood cells. Morphological abnormalities were identified and recorded using light microscopy.

Results: Significant structural alterations were observed in erythrocytes, including target cells, echinocytes, Howell-Jolly bodies, and hypochromia in the Cd-exposed group. Neutrophils showed increased nuclear lobulation and deformation. No significant change in cell morphology was observed in the control group, and normal structural features were preserved in erythrocytes and neutrophils.

Conclusion: This study shows that cadmium (Cd) exposure causes significant morphological changes in the hematological system. Erythrocyte deformations, hypochromia, and Howell-Jolly bodies suggest that Cd may increase the risk of anemia by disrupting erythrocyte membrane integrity. These changes may serve as early markers of Cd toxicity.

Keywords: Cadmium, peripheral blood smear, cadmium poisoning, blood cells, rat

Introduction

Toxic metals, particularly cadmium (Cd), accumulating in the environment as a result of industrial and agricultural activities, pose a serious threat to the health of living organisms. While Cd is naturally introduced into the environment in limited amounts, it has become a significant component of environmental pollution due to the increasing industrial applications (1, 2). Cd, widely used in nickel-cadmium batteries, steel plating, paint production, and the electronics industry, is also found as an impurity in areas such as phosphate fertilizers, detergents, and refined petroleum products (1, 3). Approximately 13,000 tons of Cd are produced annually worldwide, contributing to environmental pollution, especially in underdeveloped countries (2). Cd exposure can occur through inhalation and oral routes, leading to acute or chronic toxic effects. Short-term inhalation exposure causes pulmonary irritation in the lungs, while long-term exposure may result in toxic effects on the liver, kidneys, and the nervous, cardiovascular, and skeletal systems (4, 5). Furthermore, the accumulation of soluble Cd salts in organs has been associated with conditions such as anemia and eosinophilia (4, 6).

Another significant aspect of the toxic effects of Cd is its adverse impact on the hematological system. Cd exposure can cause marked changes in the number and morphology of blood cells. It can lead to microcytic and hypochromic anemia in erythrocytes, as well as abnormalities such as eosinophilia and lymphopenia in leukocytes (3,7). Increased oxidative stress leads to lipid peroxidation on the erythrocyte membrane and cellular deformation, thereby reducing hemoglobin transport capacity. This condition affects the delivery of oxygen to tissues and leads to disturbances in the overall metabolic balance of the organism (8). Additionally, structural changes in leukocytes weaken immune functions, increasing the organism's susceptibility to infections (9). Investigating these multifaceted toxic effects of Cd is essential for the early detection of Cd exposure through hematological parameters. Research has been conducted on the toxic effects of Cd on the hematological system and the morphological changes in blood cells; however, the extent and scope of these studies are limited. Studies on Cd toxicity have mostly been conducted at the biochemical or molecular level. Peripheral blood smear analysis is a simple and effective method to evaluate the morphological effects on blood cells.

Upon reviewing the existing literature, there have been no studies involving peripheral blood smear analysis to assess the effects of Cd exposure on the hematological system. Therefore, the aim of this study is to examine the morphological changes in blood cells induced by cadmium poisoning in a rat model.

Materials and Methods

This experimental study was approved by the Dicle University Local Ethics Committee and was conducted in accordance with ethical guidelines (Ethical approval no: 3, date: 26/01/2023).

Fourteen male Wistar albino rats (8-10 weeks old; 300-350 g) used in the study were housed under standard conditions in the Dicle University Experimental Animals Laboratory. The rats were kept in steel cages with a constant temperature between 22-25°C, a 12-h light/dark cycle. All rats were given food (standard rat chow) and water (tap water) ad libitum. The cages in which the rats were housed were cleaned once a week. A graphical illustration of the study is shown in Figure 1.

The animals were grouped into two groups, each consisting of seven rats, as follows:

Group I (Control Group): Rats in this group were given only standard diet and tap water. These rats were given 0.5 ml of physiological saline by oral gavage every day for 14 days.

Group II (Cd Group): Rats in this group were exposed to 3 mg/kg cadmium chloride ($CdCl_2$) (Merck Millipore, 202908) dissolved in 0.5 ml of water by intraperitoneal (IP) every day for 14 days (10, 11).

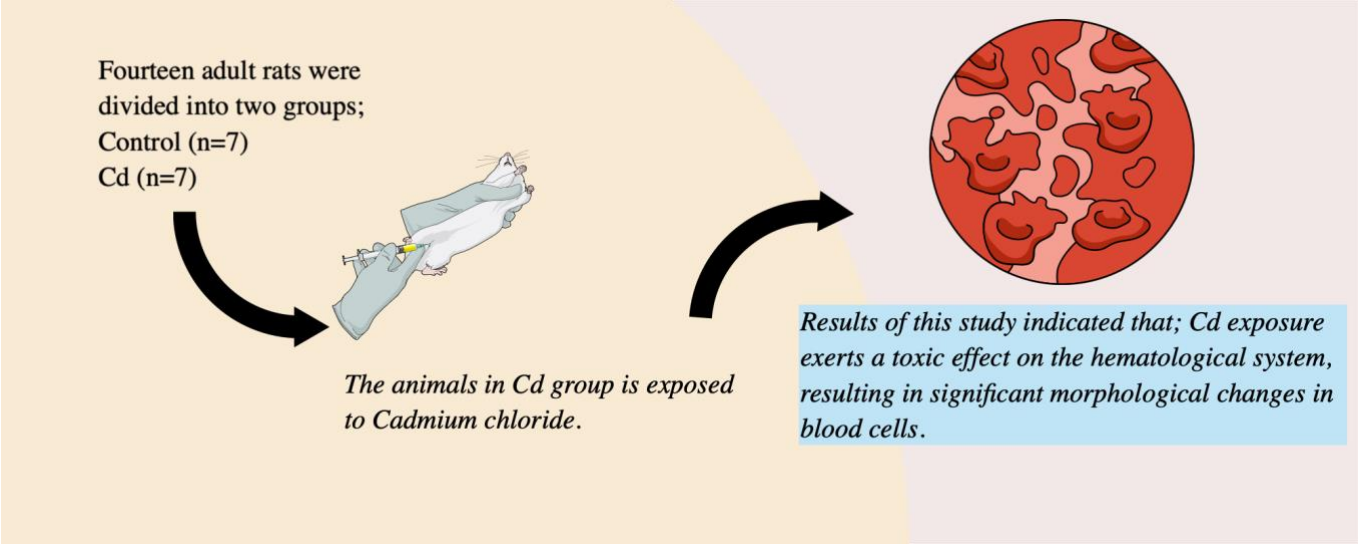

Figure 1. Graphical illustration of the study

At the end of the experimental period, rats were anesthetized after 12 hours of fasting. For anesthesia, rats were given 9 mg/kg xylazine and 90 mg/kg ketamine HCl injections. They were sacrificed under anesthesia by exsanguination, and blood samples were taken. Blood samples were prepared for peripheral blood smear analysis.

Results

Morphological changes in peripheral blood cells

Erythrocyte morphology

Structural abnormalities indicating disturbances in the erythrocyte membrane were detected in rats exposed to cadmium (Cd). Peripheral blood smears of Cd-exposed rats exhibited prominently target cells and spur cells (echinocytes/acrocytes).

Additionally, Howell-Jolly bodies were observed within the erythrocytes. The central pallor of the erythrocytes suggested a decrease in hemoglobin content (hypochromia) (Fig. 2). Numerous deformed and fragmented erythrocytes were present in Cd-exposed rats.

Neutrophil Morphology

Typical neutrophils were observed in control animals (Fig. 2). In contrast, neutrophils in Cd-exposed rats exhibited morphological changes.

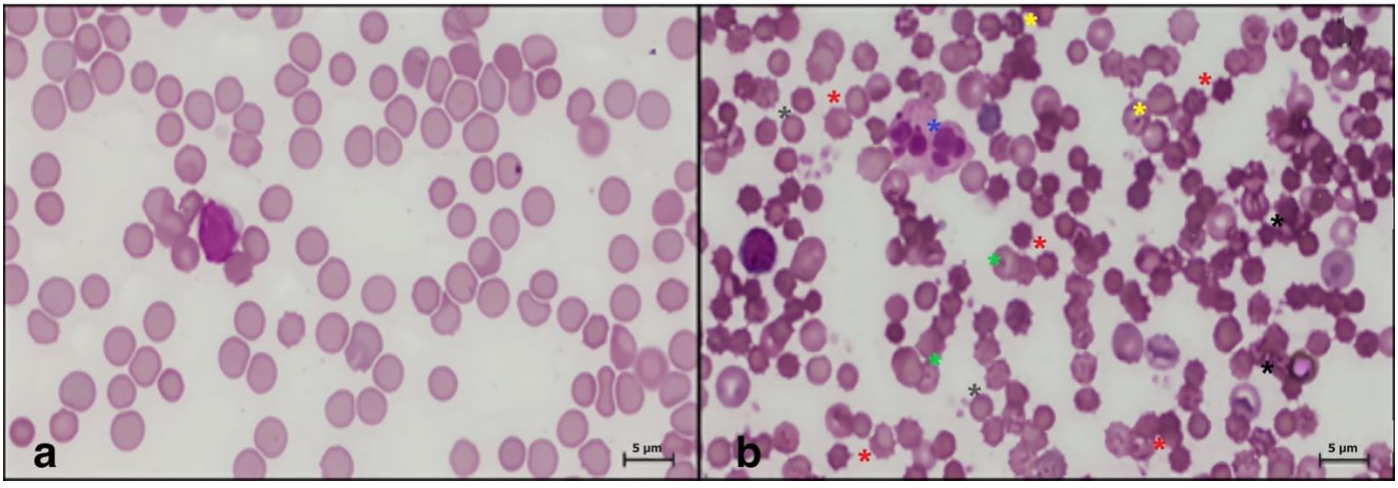

Figure 2. **a.** Normal blood cells; **b.** Target cells and spiky erythrocytes (echinocytes/acrocytes) (green, red) in peripheral blood smears of rats exposed to Cd; Howell-Jolly bodies (yellow) within erythrocytes; hypochromia (gray); numerous deformed and broken red blood cells (black); shape changes in neutrophils (blue).

Discussion

In this study, morphological changes in blood cells were evaluated by peripheral blood smear method in rats exposed to cadmium (Cd). The findings show that Cd toxicity causes significant morphological changes in blood cells.

Erythrocytes are the most abundant cell type among the cellular components of blood and play a central role in oxygen transport in the body. The transport of oxygen from the lungs to body tissues is provided by the hemoglobin content of erythrocytes. Hemoglobin is the most basic component of the oxygen-carrying capacity, and the increase in this capacity of erythrocytes is parallel to the increase in the surface area of the cells (12). However, the ability to carry oxygen is directly related to the structural integrity of erythrocytes (13). Changes in the central pallor of erythrocytes indicate an improper distribution of hemoglobin and a decrease in the oxygen-carrying capacity of the cell (12). In our study, structural abnormalities were observed in the erythrocyte membrane in rats exposed to Cd, and it is thought that these changes negatively affect the oxygen-carrying capacity of erythrocytes.

Changes in the erythrocyte membrane may indicate deterioration or potential changes in cellular physiological conditions (14). In vitro studies of CdCl2 on human erythrocytes have shown that reactive oxygen species (ROS) production is increased, antioxidant capacity of erythrocytes is decreased, and glucose metabolism is impaired. In addition, these changes were confirmed by membrane damage, increased osmotic fragility, and inhibition of membrane-bound enzymes. Microscopic examination of erythrocytes revealed the presence of cells showing echinocyte (acanthocyte) morphology (15). In our study, similar findings confirmed that Cd exposure causes serious damage to the

erythrocyte membrane and causes changes in the morphological structures of the cells. In particular, target cells and echinocytes observed in peripheral blood smears show structural deterioration of the erythrocyte membrane and deviation of the cells from their normal rounded shapes. These findings suggest that the lipid bilayer and protein structures of the erythrocyte membrane are disrupted, resulting in loss of cell elasticity (15).

The observation of Howell-Jolly bodies in erythrocytes is another important indicator that normal cellular functions are impaired. Howell-Jolly bodies are nuclear remnants that are usually found in immature or damaged erythrocytes. Under normal conditions, erythrocytes are expected to be nucleus-free. However, conditions such as oxidative stress and hemolysis can trigger the formation of these bodies (16). This is a strong finding that Cd exposure can negatively affect the development and functions of erythrocytes. Central pallor and hypochromia of erythrocytes indicate a decrease in hemoglobin content (17). In our study, the observation of deformed and broken erythrocytes suggests that hemolysis is progressing and paves the way for the development of anemia. It has been observed that Cd increases oxidative stress levels in the cell, leading to hemoglobin oxidation and cell membrane damage (18). Such structural changes negatively affect the oxygen-carrying capacity and lifespan of erythrocytes. Therefore, structural and functional changes in erythrocytes triggered by Cd exposure reveal not only its toxic effects but also the mechanisms that may lead to anemia. It has been shown in the literature that Cd can affect erythrocyte structure and hemoglobin metabolism, disrupt iron metabolism, and lead to anemic conditions, and this finding is confirmed by our study (17, 18).

White blood cells are the main components of the immune system and play a critical role in managing inflammation. Neutrophils constitute the first line of defense of the immune system and migrate rapidly to affected areas in the early stages of inflammation. The main function of neutrophils is to eliminate microorganisms by phagocytosis and secrete antimicrobial molecules. They also affect both innate and adaptive immune responses by forming neutrophil extracellular traps to support degranulation, antigen presentation, and immune responses (19). The effects of Cd on peripheral leukocytes have been extensively investigated in studies (20, 21). Xiong et al. stated that long-term Cd exposure can suppress the immune system and is particularly associated with a decrease in neutrophil numbers (21). In our study, morphological changes were observed in neutrophils in the Cd-exposed group, and these changes are consistent with the existing literature showing the negative effects of Cd on the immune system (22). The findings of our study show that Cd causes morphological changes not only in erythrocytes but also in white blood cells and has suppressive effects on the immune system. These findings show that the toxic effects of Cd have a multidimensional mechanism affecting both the hematological and immune systems.

Limitations

In the study, the conclusions that Cd causes anemia are based only on morphological findings obtained from peripheral blood smear. Therefore, additional biochemical analyses are required to determine definitively whether Cd causes anemia. In addition, the morphology of leukocytes and platelets has not been fully examined. This prevents a more detailed understanding of the changes at the cellular level. These limitations may provide a guide for future studies to use more comprehensive assessment methods.

Conclusion

This study demonstrates that cadmium (Cd) exposure has significant adverse effects on the hematological system. Morphological changes in erythrocytes and alterations in neutrophil structure are clear indicators of Cd's toxic effects. The presence of target cells, echinocytes, and acanthocytes in erythrocytes is associated with structural damage to the erythrocyte membrane due to Cd exposure. The presence of Howell-Jolly bodies suggests potential dysfunction in spleen function or disruption in erythrocyte regeneration. Hypochromia indicates a decrease in hemoglobin synthesis or a reduction in the oxygen-carrying capacity of erythrocytes. Deformed and fragmented erythrocytes strongly suggest that hemolysis plays a role in the development of anemia. These structural and functional impairments in erythrocytes are direct consequences of Cd toxicity, and the findings indicate that Cd exposure may lead to hematological disorders and, in the long term, cause health issues such as anemia.

Disclosures

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Ethical Approval: Ethics committee approval was received for this study from the Dicle University Local Ethics Committee, in accordance with the World Medical Association Declaration of Helsinki, with the approval number: 2023/3.

Peer-review: Externally peer-reviewed.

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