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Review Article

Histopathological and Physiological Study of Drug Related Hyperostosis in rat

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ABSTRACT
Hyperostosis is a condition in which there is enlargement of the outer portion of bones. However, a range of conditions in which there is thickening of the endosteal surface can also occur. The present study aims to evaluate the histopathological changes induction hyperostosis by doxorubicin on femur & joint. The experiment was done on 80 male & female rats (Rattus norvegicus) sexually mature weighing 150-200 gram, divided into 4 equal groups of 20 animals each: control group which was given distilled water while the treated animals injected with drug (doxorubicin) I/P as dose 2.5 mg/ Kg, 5 mg / Kg, & 10 mg / Kg represented low toxic dose, intermediate toxic dose, finally high toxic dose respectively for sex month.
The animals scarified after six months then the femur and joint taken to prepared histopathological slides and examined to observe the pathological changes that induction by drug. The present aimed to study pathophysiological changes of doxorubicin on the bone tissues of femur and joint in the rats.

Keywords: hyperostosis, drug, doxorubicin, femur, rats

INTRODUCTION

Hyperostosis is a term used to show an unusual increment in the solidification of the skeleton, yet not relevant to versatile changed, for example, those in size and mass of bones identified with expanded mechanical work (an over the top development or thickening of bone) (Revell, 1986). Osteoscslerosis is, be that as it may, included with the term hyperostosis, being characterized as an expansion in bone thickness without adjustment in the general state of the influenced bone, such a change is seen in renal osteodystrophy (Arcamone et al.,1969).
Doxorubicin (Adriamycin or DOX), a topoisomerase II focusing on medicate, is one of the best chemotherapeutic operators utilized in the facility to treat malignancy since its detachment in 1960s from Streptomyces peucetius ((Arcamone et al.,1969; Weiss, 1992). DOX is as one the best chemotherapy specialists utilized either alone or related to different medications or radiotherapy to treat various sorts of dangerous neoplasia. Doxorubicin (DOX) is an anthracycline anti-microbial that is utilized as an antineoplastic operator in hematological, just as in strong malignancies, because of its high antitumor viability (Mross, 1991; Hortobagyi, 1997; Bonadonna et al., 1998; Dollery, 1999; Gewitz, 1999; Minoti et al., 2004; Ahmed et al., 2010). Notwithstanding, its clinical use is constrained by the myelosuppressive impacts and advancement of irreversible cardio-toxicity, just as its capacity to cause malignancy cell obstruction during treatment (Saad et al., 2000; Martindale, 2011). Stomatitis, gastrointestinal (GI) unsettling influences, and alopecia are normal, however reversible.
Doxorubicin (DOX) is an extremely proficient antitumor medication, yet its organization is restricted by a portion needy, irreversible, and dynamic cardiomyopathy, which may become obvious years after consummation of the treatment (Steinherz et al., 1991; Grenier and Lipshultz, 1998; Dudka et al., 2009; Fulbright, 2011; Feola et al., 2011). The patho-mechanism of DOX-related late cardio-toxicity is multifactorial (Minotti et al., 2004; Korga et al., 2012), yet the predominant speculation credits the prevailing job to oxidative pressure connected to redox-cycling of the medication (Doroshow, 1983; Xu et al., 2001). The DOX redox-cycling is begun from one-electron decrease with the development of DOX radical (DOX∗) (Bachur et al., 1978). These receptive oxygen species (ROS) are answerable for oxidative pressure. The previously mentioned chemicals engaged with DOX creation are bountiful in hepatocytes (Crib et al., 2005), recommending that liver might be particularly associated with DOX age. Albeit no such extreme DOX synthase happens in the heart, generally low cancer prevention agent safeguard of cardiomyocytes makes the heart an objective for DOX poisonousness (Berthiaume and Wallace, 2007).

MATERIAL AND METHOD

The current investigation analyze was directed in the research facility creatures' place of Veterinary Medication School - College of Basrah. Where 80 male and female white rodents (Rattus norvegicus) explicitly develop and (150-200) gram weighting, were utilized. The creatures were obliged in a similar lab condition by keeping them in unique pens. The room temperature was set between 20-25 ºC. The supplement for rodents was pellet and watered libitum.

The examination accomplished for a half year as toxological pathology concentrate on 80 rodents that divided to four equivalent gathgerings, each gathering comprise of (20 rodents) of both sex that contains 10 male and 10 females. The creature bunches rewarded with doxorubicin as I/P infusion as 2.5 mg/Kg b. w. was low harmful portion, 5mg/Kg b. w. was halfway portion, and 10 mg/Kg b. w. was high poisonous portion of doxorubicin, at long last the fourth gathering as control that gives distal water just for a half year. Toward the finish of the analysis, the creatures scarified then the femur and joint were taken, at that point fixed in 10% formalin going on for about fourteen days. Histological area were produced using femur and joint after decalcification by utilizing at that point recolored with (H and E) stain (Roach et al., 2003).

RESULTS

After administration by doxorubicin there are abnormal bone formation on major long bones femur, lesions characterized by growth of parallel trabeculae which extended and expand as cavities with bone formation and which we see as excessive in figure (1, 2, 3, & 8) but these histological features are moderate in (4, 5, & 6).

The pathological changes in the femur bone show presence of an active chondrocytes cell layer, absence of proliferating chondrocytes, & zone of chondrocyte hypertrophy of growth plate. Presence of trabeculae into the epiphyses in high toxic dose group (figure 1). The presence of high osseous tissues (hyperostosis) with Haversian canal clearly appear in high toxic dose group (figure 2). The figure 3 shows presence of trabecular bone & Haversian canal that formed into the epiphysis of high toxic dose group. Pathological changes into the moderate toxic dose group that found the new bone growth that extend to outside direction to word muscle tissues (exostosis) in figure 4. Figure 8 represent as high toxic dose group that show secondary ossification appear into the epiphysis with hypertrophic chondrocyte zones, very clear trabecular bone forming with mineralization in (figure 8).

The result appears in moderate toxic group animals that reveals new or compact bone tissues on the right side as the new growing tissues and the bone marrow into the left side with active osteoblast on the bone surface and osteocyte into the lacunae shows in (figure 5). The result appears in moderate toxic group animals that reveals new or compact bone tissues as the new growing tissues (hyperostosis) as show in (figure 6). The pathological changes as excessive bone formation osseous tissues as hyperostosis without or absence of Haversian canal (compact tissues) in (figure 7).

The pathological changes found in figure (9 & 10) that represent low toxic dose group presence of osseous tissues, osteocytes into the bone tissues in high number, and Haversian canal in (figure 10) only as low toxic dose group in both.

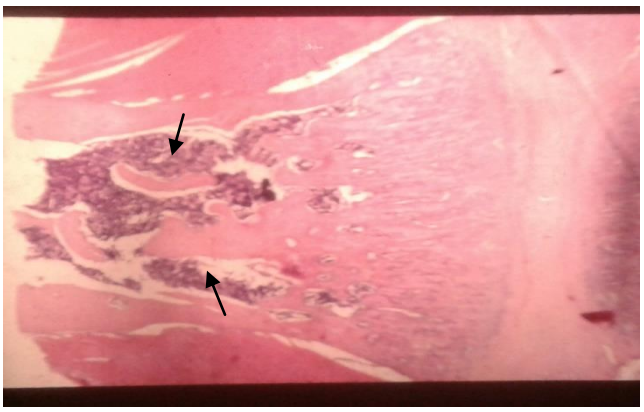

Fig. 1: Section in femur bone & joint administered 10 mg/ kg doxorubicin show abnormal periosteal bone formation (hyperostosis) (arrow) with H & E Stain (10 X).

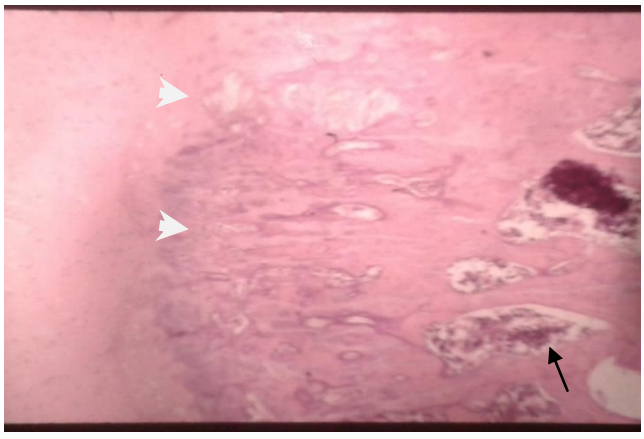

Fig.2: Section in femur bone & joint administered 10 mg/ kg doxorubicin show marked excessive bone tissue formation (hyperostosis) (arrow) and degeneration of chondrocytes (head arrow) with H & E Stain (4 X).

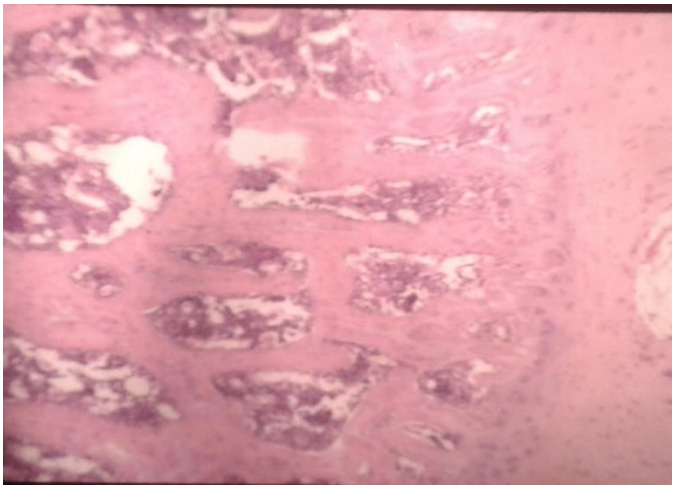

Fig.3: Section in femur & joint administered 10 mg/ kg doxorubicin show excessive formation of bone tissue hyperostosis with H & E stain (10 X).

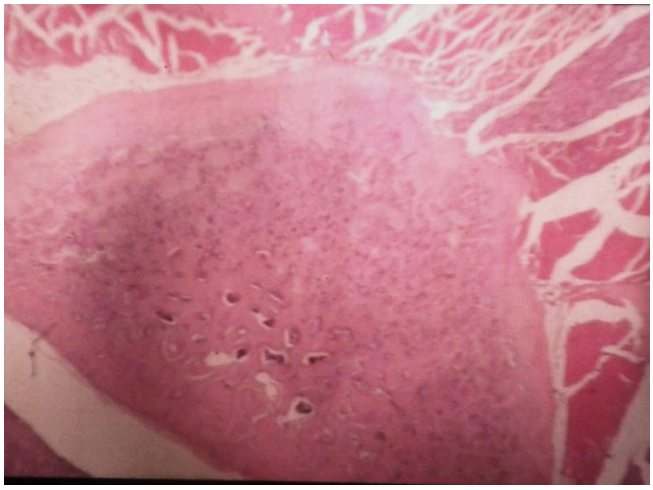

Fig.4: Section in femur & joint administered 5 mg/ kg doxorubicin show moderate formation of bone tissues exostosis (arrow) with H & E stain (4 X)

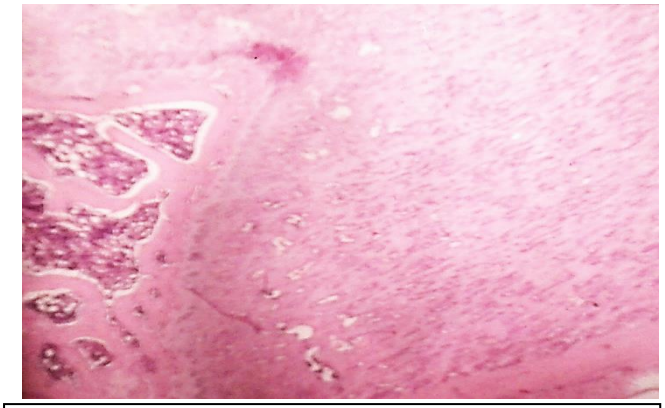

Fig. 5: Section in femur & joint administration of 5mg / kg of doxorubicin show moderate formation of bone tissues hyperostosis with H & E stain (10X).

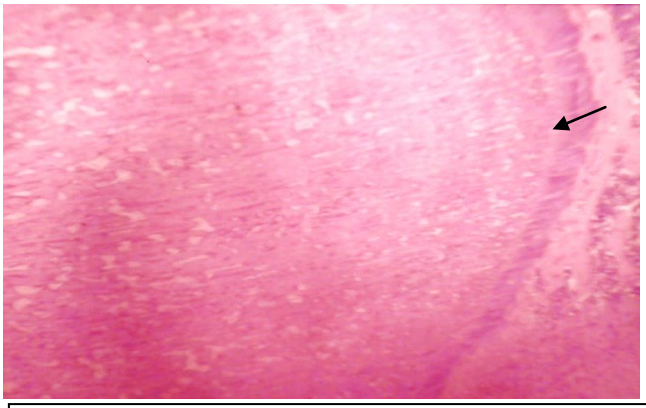

Fig. 6: Section in femur & joint administration of 5mg / kg of doxorubicin show moderate formation of bone tissues hyperostosis with H & E stain (4 X).

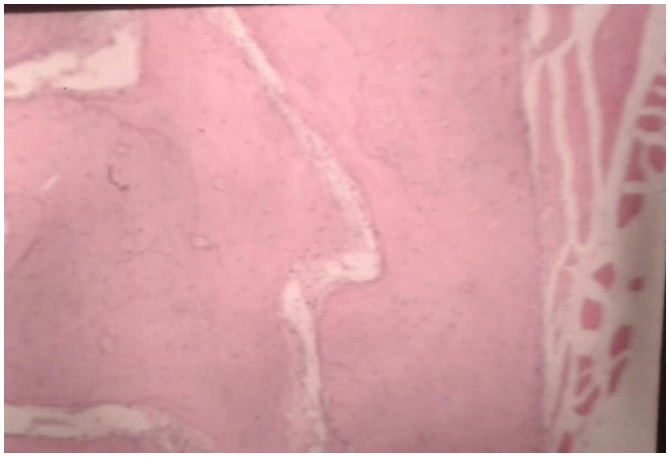

Fig. 7: Section in of femur & joint administration of 5mg / kg of doxorubicin show mild formation of bon tissues hyperostosis with H & E stain (4 X).

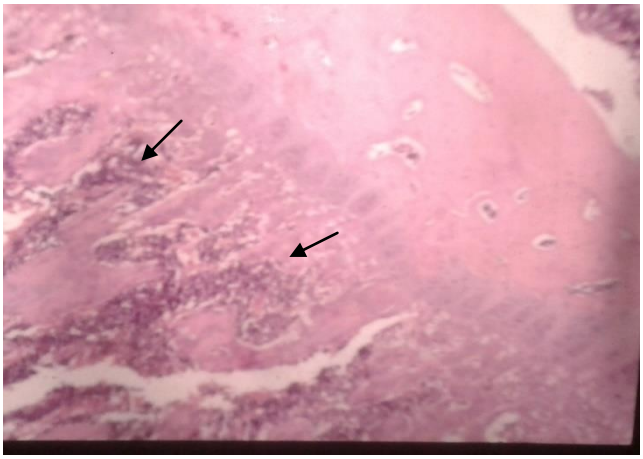

Fig. 8: Section in femur & joint administration of 10 mg / kg of doxorubicin show excessive formation of bone tissues hyperostosis (arrow) with H & E stain (10 X).

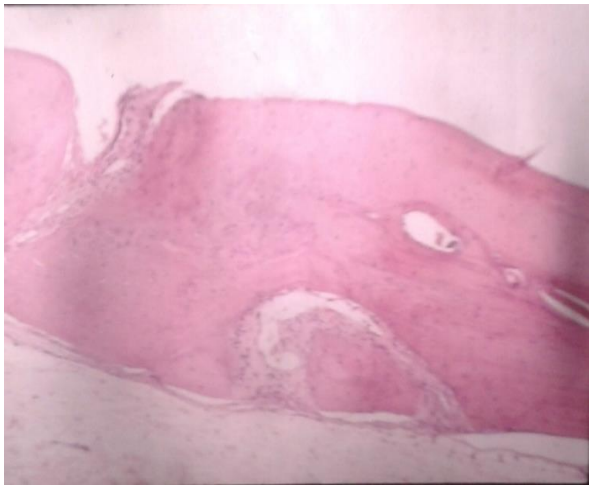

Fig. 9: Section in femur & joint administration of 2.5 mg / kg of doxorubicin show low formation of bone tissues with H & E stain (4 X).

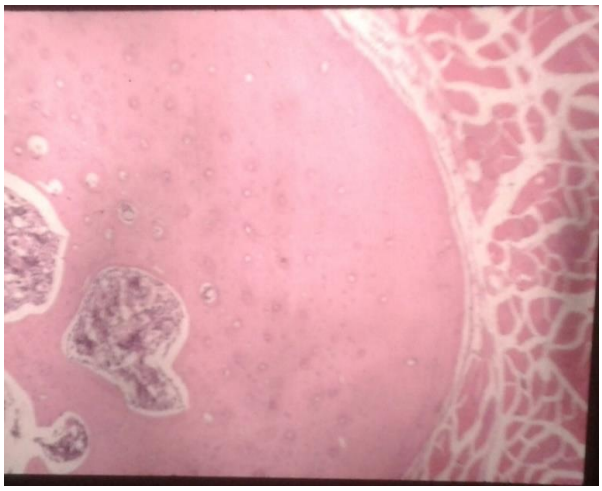

Fig. 10: Section in femur & joint administration of 2.5 mg / kg of doxorubicin show low formation of bone tissues with H & E stain (10 X).

DISCUSSION

DOX instigates the age of ROS during the redox cycling of its quinone moiety; it likewise upsets iron digestion, though harmful DOX metabolites are delivered in the heart and hematopoietic tissue (Kim et al., 2009; Zhang et al., 2012). Oxidative pressure triggers the inborn mitochondria-subordinate apoptotic pathway in cardio-myocytes and hematopoietic cells. The aftereffects of this examination indicated that there is poisonous impacts because of utilizing of doxorubicin tranquilize which utilized as antitumor medication spoke to by appearance of strange developing of the bone and aggravation with bone resorption (Kluza et al., 2004).

As it's known doxorubicin (DOX) viewed as a typical medication in chemotherapy because of its adequacy in battling a wide scope of malignancies, for example, sarcomas, carcinomas and hematological diseases however this medication can be a twofold edge blade since its poisonous results on heart, cerebrum, kidney, liver and others (Carvalho et al., 2009), through discharges receptive oxygen species (ROS) (Rivakar, 2014). ROS lead to oxidative pressure, DNA harm, lipid peroxidation and layer harm and triggers apoptotic pathways of cell passing (Thorn et al., 2011), notwithstanding bone illnesses (Garrett et al., 1990), which is one of the most significant ailments have been connected to oxidative pressure (Domazetovic et al., 2017).

Regardless of the redox state is assume job in bone renovating process by means of the persistent bone recovery through the organized activity of bone cells: osteoclasts, osteoblasts and osteocytes, yet any adjustments in ROS and additionally cancer prevention agent frameworks lead to pathogenesis of bone (Zarkovic, 2020).

An overproduction of ROS could be results from physiological occasions, for example, maturing and hormonal changes (reduction of estrogen) or neurotic occasions identified with the creation of incendiary cytokines associated with numerous obsessive procedures, exogenous and endogenous poisons, radiation presentation and medication treatments (Guo et al., 2011).

Along these lines, obviously utilizing of DOX as against malignant growth tranquilize for a half year discharged enormous measures of responsive oxygen species and that caused appearance of strange developing of bone as happen in the outcomes, particularly the time of medication organization is a similar time of the physiological procedure wherein osteoclasts dispense with old or harmed bone tissue which is in this way supplanted with new bone tissue framed by osteoblasts (Garrett et al., 1990).

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