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Histopathologic Study on The Toxic Effect of Aluminium Chloride on the Heart, Liver and Kidneys of Rabbits

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ABSTRACT

The present study was designed to investigate the adverse effects of aluminum chloride hexahydrate on the heart, liver and kidneys of rabbits. Twenty-four apparently healthy male and female rabbits were randomly assigned to four groups. The two control groups male (n= 6) and female (n= 6) received subcutaneous injections of physiological saline. The other two Al-treated groups of male (n= 6) and female (n= 6) were given 2.5mg/kg B.W. S/C five times per week for 3 months. At the 6th weeks and the 12th weeks, three rabbits from each group were necropsied and tissues specimens from heart, liver and kidneys were collected and processed for the following histopathologic examination. The heart of both sexes of intoxicated rabbits showed congestion of blood vessels, interfibrillar edema, hemorrhage as well as Zenker's degeneration and necrosis of myocardium. The Liver showed periportal edema, mild fibroplasia, infiltration of inflammatory cells, adenomatous and papillary hyperplasia of bile ductules. The encountered lesions of the kidneys were in the form of vacuolations and necrosis of renal tubular epithelium, with intratubular necrotic cellular debris and hyaline casts. An additional lesion of severe interstitial nephritis was also seen in some areas. It was concluded that the adverse toxic effects of aluminum chloride were time-dependent manner on heart, kidneys and liver of of both sexes of rabbits.

1. INTRODUCTION

Human and animals are daily interact with their environment and exposed to broad spectrum of chemicals and heavy metals like aluminum, mercury, lead and cadmium which are belonging to the most important hazardous substances that can bioaccumulate in the body and collected in tissues with low execration (Ali and Amin, 2006).

Aluminum is an ubiquitous element and is the third most prevalent element in the earth's crust, comprising approximately 8% of the earth's crust, exceeded by oxygen (47%) and silicon (28%) and one of the most remarkable elements in the periodic table (Verstraeten et al., 2008). In the medicine field, aluminum compounds are now widely used in the composition of numerous pharmaceutical conditionings such as antacids, phosphate binders, toothpaste, aspirins, vaccines and antiperspirant (aluminum chloride hexahydrate). Moreover, purification purposes of water and Food additives making them a potential threat (Shaw and Tomljenovic, 2013).

Much of the aluminum that enters the human body comes from the food and water and a smaller amount enters through the skin, such as in antiperspirants and most of this aluminum is rapidly removed by the kidneys which leading to renal dysfunction (Becaria et al., 2002). To date, the main known toxicological effects of aluminum included microcytic hypochromic anemia (Eman et al., 2013), neurodegenerative disorders such as Alzheimer disease, amyotrophic lateral sclerosis and dialysis encephalopathy (Goncalves and Silva, 2007), hepatotoxicity (El-Sayed et al., 2011), genotoxicity (Kakimoto et al., 2005 and Vieželienė et al., 2006) and diverse effects on both male

reproductive system (Yousef et al., 2007) and female ovaries (Fu et al., 2014) .The toxic effects associated with aluminum are due to the generation of reactive oxygen species (ROS) (Türgut et al., 2006 and Yuan et al., 2012) and DNA oxidative deterioration (Sargazi et al., 2006).

2. MATERIALS AND METHODS

2.1 Animals and experimental design

Twenty-four apparently healthy V-line rabbits (3 to 4 Kg) (12females and12 males) were procured at age of 2 years from a closed bred colony at College of Agriculture, Alexandria University, Matrouh branch, Egypt. They were housed under recommended environmental conditions and the basal diet up to two weeks before the experiment for adaptation. Rabbits were received human care in compliance with the guidelines of the National Institutes of Health (NIH) of Animal Care and the local committee approved this study. The animals had free access to a standard pellet diet and drinking water. The animals were randomly assigned to four groups for 3 months. The first control group (6 females) received subcutaneous injections of physiological saline. The second Al- treated group (6 females) received 2.5mg/kg B.W. S/C five times per week from aluminum chloride hexahydrate (Duval et al., 1986). Aluminum chloride was purchased from Algomhuria Co. Egypt. The third control group (6 males) received subcutaneous injections of physiological saline. The fourth Al-treated group (6 males) received 2.5mg/kg B.W. S/C five times per week from aluminum chloride hexahydrate.

2.2 Histopathologic studies

After necropsy at the 6^{th} and the 12^{th} weeks, the heart, liver and kidneys were removed and then rapidly fixed in 10% neutral buffered formalin solution for at least 24 h. The fixed specimens were processed through the conventional paraffin embedding technique. Paraffin blocks were prepared then5 microns thick sections were obtained. These sections were stained with Hematoxyline and Eosin (H&E) according to the method described by Bancroft et al. (2013).

3. RESULTS

3.1. Histopathologic examination

3.1.1 Heart

The heart of control female and male rabbits had normal histologic limits. The heart of aluminum treated female rabbits, after the 6^{th} weeks, showed congestion of blood vessels, interfibrillar edema and hemorrhage and Zenker's degeneration of myocardium that was represented by accumulation of hyaline material in the myocardial sarcoplasm leading to hypereosinophilia and nuclear pyknosis without any inflammatory reaction (Fig.1 A). While after the 12^{th} weeks, the sarcoplasm of degenerated myocytes exhibited variable size diffuse myocardial empty vacuoles of fatty type (Fig. 1 B). Moreover, there was interfibrillar hemorrhage and edema (Fig. 1 C) with infiltration of inflammatory cells. Zenker's necrosis of myocardium was also seen which characterized by an increase of cytoplasmic eosinophilia, hyaline accumulation, and loss of muscle striation with nuclear pyknosis and infiltration of inflammatory cells predominantly lymphocytes (Fig. 1 D). But the heart of male rabbits showed, after 6 weeks of the experiment, congestion of blood vessels (Fig. 1 E). Furthermore, multifocal lytic necrosis was observed in some myocardial fibrils (Fig. 1 F).After the 12^{th} weeks of the experiment: There was moderate congestion of blood vessels and severe interstitial myocarditis associated with mononuclear cell infiltrates (Fig. 1 G). Myocardial degeneration represented by sarcoplasmic vaculation of lipid type (Fig. 1 H) with Zenker's degeneration. In addition to intermyocardial hemorrhage was seen.

3.1.2 Liver

Livers of control female and male rabbits had normal histological structure. Conversely, the liver of Al-treated female rabbits after the 6^{th} weeks showed periportal edema, mild fibroplasia and infiltration of inflammatory cells predominantly lymphocytes (Fig. 2A). In addition to congestion of portal veins with mild fibroplasia and inflammatory cells infiltration (Fig. 2B) were noticed. After the12^{th} weeks liver showed dilatation of hepatic sinusoids and portal veins which engorged with blood with mononuclear cells infiltration in the periportal area (Fig. 2C). Another periportal area showed adenomatous and papillary hyperplasia of bile ductules with the mild proliferation of connective tissue (fibroplasia) (Fig. 2D). Moreover, hepatocellular necrosis was less frequent. While the liver of aluminum treated male rabbits after the 6^{th} weeks of the experiment revealed periportal infiltration of inflammatory cells especially lymphocytes with mild fibroplasia were evident (Fig. 2E). The affected hepatocytes had moderate cytoplasmic vacuolation in periportal and mid-zonal that appeared mostly of hydropic type (the hepatocyte cytoplasm had foamy or feathery appearance) (Fig. 2F) and rarely of the lipid type (the hepatocyte cytoplasm had multiple discrete vacuoles with sharp or distinct borders). After the 12^{th} weeks of the experiment, the hepatic sinusoids and central veins were moderately dilated and engorged with blood with mononuclear cells infiltration of lymphocytic type (Fig. 2G). Moreover, there were diffuse centrilobular and mid-

zonal (paracentral) hepatocytic vacuolation. The cytoplasm of degenerated hepatocytes appeared foamy or feathery that indicative of hydropic degeneration (Fig. 2H).

3.1.3 Kidneys

The renal tissue of control female and male rabbits had the normal morphology of renal parenchyma with well-defined glomerular tuft and tubules. On the other hand, the noticeable renal lesions of the aluminum-treated female group after the 6thweeks were widening of the Bowman's space at the expense of glomerulus leading to increased urinary spaces and necrosis of glomerular capillary tufts. Approximately, 10% of available cortical tubules showed changes ranging from tubular epithelium attenuation to necrosis. The non-necrotic degenerated renal tubular epithelium exhibited vacuolar degeneration which characterized by swollen of tubular epithelium and had foamy granular cytoplasm while the attenuated tubules had very thin epithelium with karyorrhectic or pyknotic nuclei. And other degenerated tubules showed cloudy swelling which characterized by enlargement of epithelial cells toward the tubular lumen rendering the lumen narrow and had a star shape. Moreover, the necrotic renal tubules had dark eosinophilic necrotic debris (Figs. 3A). There was congested blood vessel with intratubular hyaline casts formation (Fig. 3B). After the 12th weeks of the experiment, interstitial nephritis with severe inflammatory cells infiltration and necrosis of tubular epithelium were observed (Fig. 3C). The glomerular lesions were in the form of atrophy of glomerular tuft with subsequent widening of Bowman's space associated with shedding of tubular epithelium and mild interstitial fibroplasia with little inflammatory cell infiltration (Fig. 3 D).Regarding to the renal lesions of male rabbits after the 6th weeks of the experiment, there were necrosis of some cortical tubules which replaced by RBCs and the distention of glomerular capillary tuft due to proliferation of mesangial cells and mesangiolysis of mesangium leading to narrowing of Bowman's capsule and ischemic glomerular necrosis (Fig. 3E). Some of the degenerated renal tubules showed attenuation and others showed vacuolar degeneration surrounded by mild interstitial infiltration of inflammatory cells (Fig. 3F). In addition to some glomerulus was atrophied and others become necrotic and the glomerular filtrates were seen inside the Bowman's space (Fig. 3G). After the 12th weeks of the experiment, the renal tubular epithelium was necrotic with the presence of eosinophilic necrotic debris in the lumen associated with atrophy of glomerular capillary tufts and congestion of intertubular blood vessels (Fig. 3H).

4. DISCUSSION

The present study was undertaken to determine the cardiotoxic, hepatotoxic and nephrotoxic effects of aluminum chloride, in male and female rabbits by examining different histopathologic changes. Our results were spotted on changes in the heart, kidneys and livers. The rabbits were found to be more sensitive to aluminum toxicity than rats even at small doses, as the same dose of our experiment injected intraperitoneal by Chagnac et al. (1987) in rats and they did not observe any changes during examination by the light microscope. So, it appears that the toxicokinetics of aluminum chloride is dose and species dependent.

Aluminum is widely used in a number of pharmacological and cosmetic products especially aluminum chloride hexahydrate which is one of the most widely used as an antiperspirant, it forms insoluble aluminum hydroxide polymer gel plugs within sweat ducts to prevent sweating (Ganrot, 1986). Aluminum is absorbed by several routes (oral, intranasal, transdermal and parenteral). The bioavailability of aluminum from drinking water is approximately 0.1% (Walton, 2007 and Walton, 2009). The absorption of aluminum from the diet is reported to be between 0.01% and 0.04% (Greger et al., 1992). Transdermal absorption of aluminum has been reported after a single underarm application of Al hexahydrate, the absorption was found to be 0.012% of Al applied (Flarend et al., 2001). It has been reported that aluminum accumulates in all tissues of mammals such as the heart, liver, kidneys, blood, bones and brain (Al Kahtani, 2010) and it was found that one of the main organs targeted by Al exposure is the kidneys which play a major role in preventing accumulation of Al by excreting it throughout urine (Stoehr, 2006). Moreover, the toxic effects of aluminum mediated by damage to cell membranes in which aluminum bind to the ferric iron-carrying protein transferrin so it reduces binding of ferrous iron. The intracellular increase in ferrous iron led to peroxidation of lipid membrane subsequent membrane fluidity, changes in membrane potential, an increase in membrane permeability and alterations in receptor functions (Nehru and Anand, 2005).

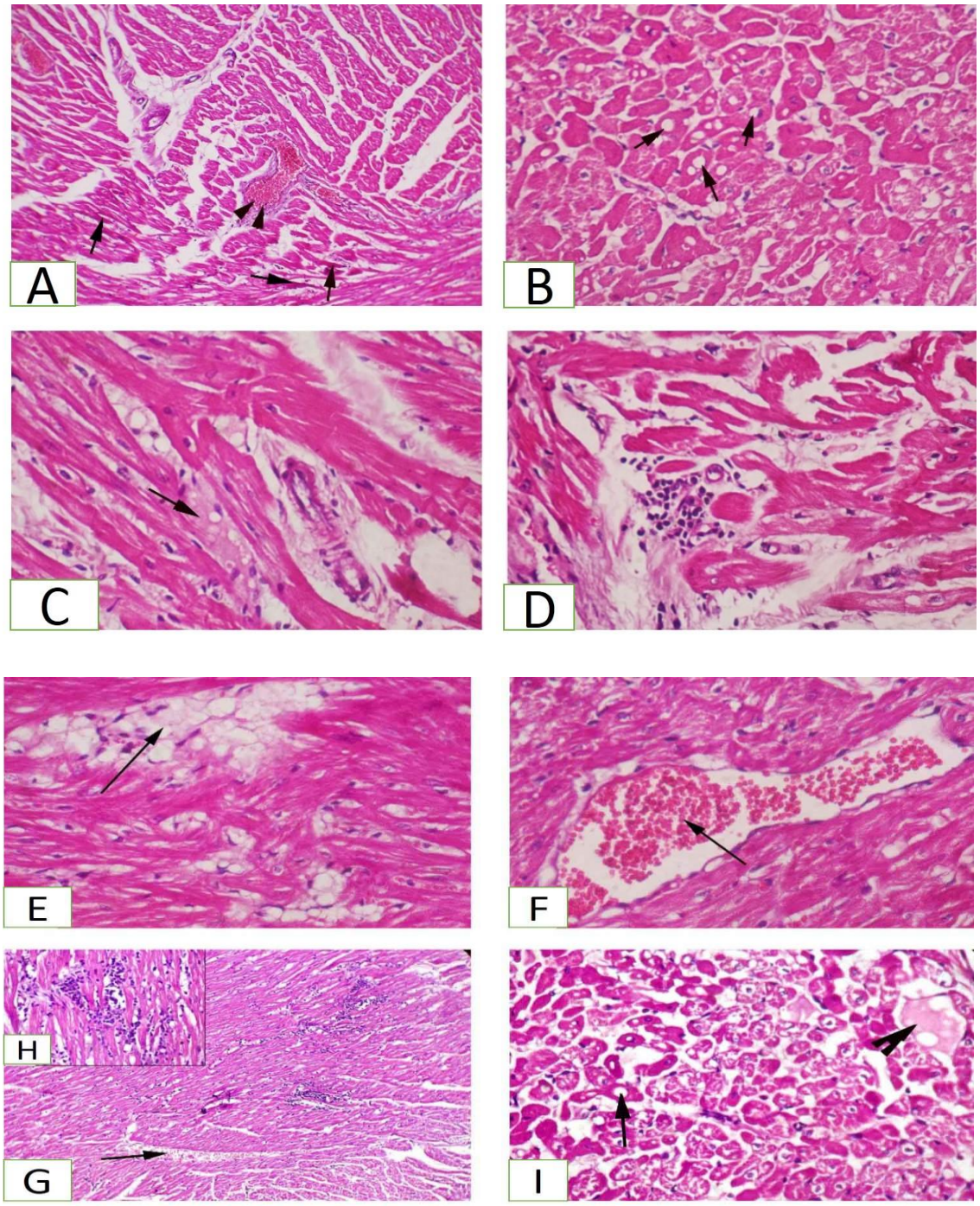

Figure (1): Photomicrograph of heart from treated female and male rabbits stained with H&E. The heart of female showing (A) Vascular congestion (arrowheads) with degenerated myocytes (arrows) after the 6th weeks. X100; (B) Myocardial vacuolation after the 12th weeks X400; (C) Interfibrillar edema (arrow) after the 12th weeks X400; (D) Necrotic area with an increased sarcoplasmic eosinophilia, nuclear pyknosis and inflammatory cell infiltration after the 12th weeks X400. The heart of male showing (E) Multifocal lytic necrosis of myocardium (arrow) after the 6th weeks X400; (F) Vascular congestion (arrow) after the 6th weeks X400; (G) Severe interstitial infiltration of inflammatory cells with vascular congested (arrow) after the 12th weeks G (X100) and H (X400); (I) Degenerated myocytes with sarcoplasmic vacuoles (arrow) and interfibrillar edema (arrowhead) after the 12th weeks X400.

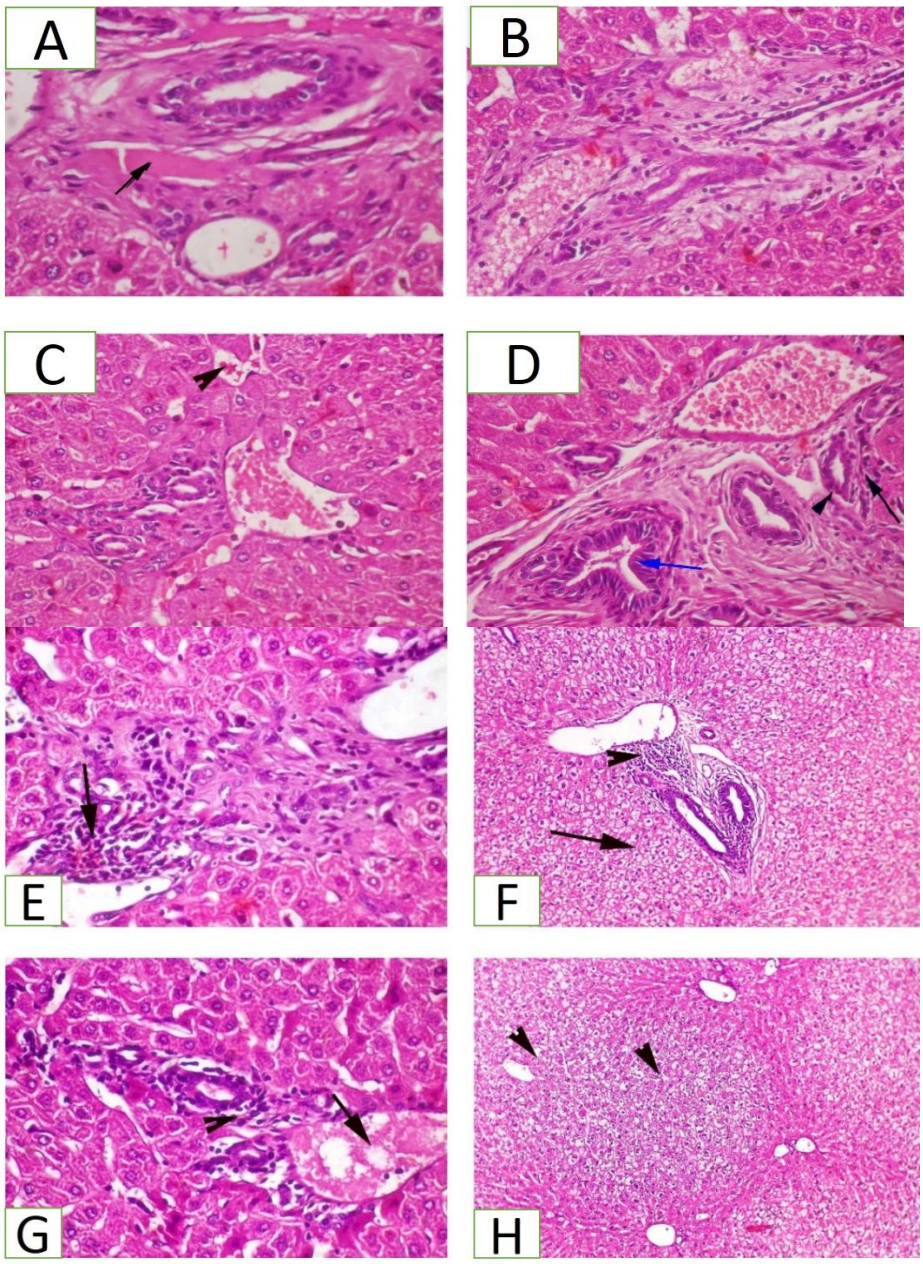

Figure (2): Photomicrograph of liver from treated female and male rabbits stained with H&E. liver of AL-treated female rabbits showing (A) Periportal edema (arrow), mild fibroplasia and infiltration of inflammatory cells after the 6th weeks X400. (B) Congestion of portal veins with mild fibroplasia and inflammatory cells infiltration after the 6th weeks X400. (C) Congestion and dilatation of hepatic sinusoids (arrow head) with mild periportal infiltration of inflammatory cells after the 12thweeks X400; (D) Papillary (blue arrow) and adenomatous hyperplasia (arrow head) of bile ductules, mild fibroplasia and interstitial infiltration of few inflammatory cells (black arrow) beside congested portal vein after the 12th weeks X400. Liver of AL-treated male rabbits showing (E) Periportal infiltration of inflammatory cells (arrow) with mild fibroplasia after the 6thweeks X400; (F) Periportal hepatocytic vacuolation (arrow) and inflammatory cell infiltrates (arrowhead) after the 6thweeks X160; (G) Congestion of portal vein (arrow) with infiltration of inflammatory cell (arrowhead) after the 12th weeks X400; (H) Paracentral hebatocytic vaculation (arrowheads) after the 12th weeks X160.

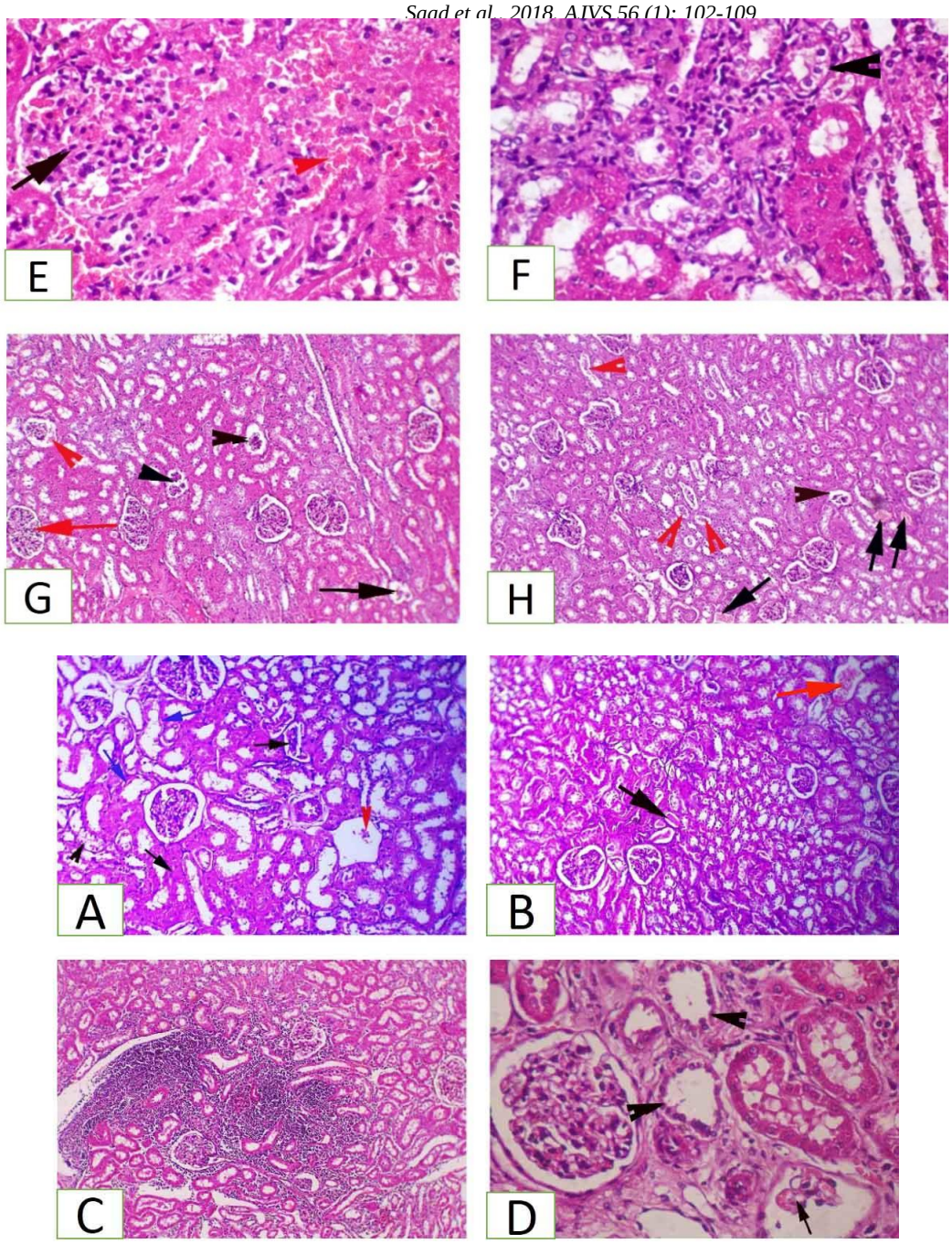

Figure (3): Photomicrograph of kidneys from AL-treated female and male rabbits stained with H&E. Kidneys of female rabbits showing (A) Vacuolar degeneration in the cortical tubular epithelium (black arrowhead), tubular attenuation (blue arrows), necrotic renal tubules (black arrows) and the remnant of necrotic glomerular capillary tuft (red arrowhead) after the 6th weeks. X200. (B) Congested blood vessel (red arrow) and intratubular hyaline casts formation (black arrow) after the 6th weeks X160. (C) Interstitial nephritis with severe mononuclear cells infiltration after the12th weeks X200; (D) Necrotic glomerular capillary (black arrow), necrosis of renal tubular epithelium (arrowheads) with the mild interstitial proliferation of connective tissue and infiltration of few inflammatory cells after the 12th weeks X400. Kidneys of male rabbits showing (E) Glomerular (arrow) and tubular necrosis after the 6th weeks X400; (F) Vacuolation of renal tubular epithelium (arrowhead) and necrosis with interstitial infiltration of inflammatory cells after the 6th weeks X400; (G) Atrophy of glomerular tufts (arrowheads) compared to normal one (red arrow), necrotic glomerulus (black arrow) with presence of glomerular filtrate in Bowman's capsule (red arrowhead) after the 6th weeks X160; (H) Congestion of intertubular blood vessels (black arrows), necrosis of renal tubules (red arrowheads) with a trophy of glomerular capillary tufts (black arrowhead) after the 12th weeks X160.

In spite of extensive documentation of toxic effects of aluminum toxicity in either animal or human, although human is daily exposed to Al from drinking water, foods and drugs. Few studies on aluminum-induced cardiotoxicity were found. Histopathologic findings of the heart in Al-treated female and male rabbits at both scarifications revealed congestion of blood vessels, Zenker's degeneration, sarcoplasmic vacuolization, myocardial Zenker's necrosis with interfibrillar edema and hemorrhage. Also male rabbits exhibited interstitial myocarditis and mild fibrosis. The same results were described by Majeda (2015). In the present study, the hepatotoxic effects of $AlCl_3$ in both sex rabbits were dilatation of hepatic sinusoids and portal veins and engorgement with blood. In addition to periportal fibroplasia, edema, biliary hyperplasia with infiltration of inflammatory cells and hepatocytic vaculation. The current hepatic lesions were parallel to those reported by Kutlubay et al. (2007), El-Sayed (2011), Buraimoh et al. (2012), Goma and Tohamy (2016) and oda (2016). Aluminum nephrotoxicity can occur when the urinary bladder is irrigated with 1% alum to treat bladder hemorrhage so it occurs in patients who have renal insufficiency Phelps et al. (1999). Regarding aluminum-induced renal damage in both sex rabbits at both scarifications, there were congestion of intertubular blood vessels and glomerular capillary tufts with attenuation and necrosis of tubular epithelium particularly proximal convoluted tubules. These results are consistent with those results reported previously by Al Kahtani et al. (2014) and Hong et al. (2000). The glomeruli of aluminum treated female and male rabbits showed ischemic glomerular collapse and mesangiolysis like observed in a variety of glomerular diseases including thrombotic microangiopathies (e.g., preeclampsia, hemolytic uremic syndrome), toxic glomerulopathy and in renal transplantation Paueksakon et al. (2002). Aluminum greatly stimulated interstitial fibrosis and severe infiltration with the inflammatory cells in male rabbits at end of the experiment similar finding reported by Somova et al. (1997).

In conclusion, this study shows that the rabbits are sensitive to aluminum toxicity. The histopathologic changes were indicative for that the S/C intoxication with 2.5 mg/kg of $AlCl_3$ which had adverse toxic effects on heart, liver and kidneys of both sexes of the rabbits especially in the male.

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