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Study the Effect of Gabapentin on the Histology of Some Organs of Male rats

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ABSTRACT

Background: Gabapentin is 1-(amino methyl) cyclohexane acetic acid with a molecular formula C9H17NO2. It used for the treatment of epilepsy, neuropathic pain, treatment of uremic pruritus, post-herptic neuralgia, and others.
Materials and methods: Eight adults white male rats were used, five of these animals were treated orally with Gabapentin 300 mg/ day, while three rats were used as a control and treated with DW.
Results and discussion: According to the histological sections, results showed no serious effects in the histology of liver, kidney, pancreas and spleen, and there is a few lymphocyte infiltrations have been observed in the liver tissue. These results were found to be compatible with previous studies, and this may reflect the safety of gabapentin regarding the histology of liver, kidney, pancreas and spleen.

Keywords: Gabapentin, rat, liver, kidney, pancreas, spleen, histology

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INTRODUCTION

The historical view of gabapentin is represented by the discovery of the anticonvulsant or antiepileptic effects. The initial clinical works on gabapentin, was given in low drug doses and then the effectiveness was determined as an add-on therapy. Patients with epilepsy were firstly treated with some anticonvulsants medications, then gabapentin was used[1,2]. Other uses of gabapentin (nonepileptic) can be demonstrated in the neuropathic pain[3, 4], also its efficiency has been represented in the treatment of uremic pruritus[5,6] diabetic neuropathy[7], post-herptic neuralgia (as it was confirmed by the Food and Drug Administration of US)[8] , chemotherapy (reducing nausea)[9], redicalopathies, trigeminal neuralgia[10,11,12], also gabapentin has been used effectively in the treatment of alcohol withdrawal in alcoholics[13,14].
Many times, the long-term treatment can lead to the occurrences of various adverse reactions of the drug [15]. Generally the administration of the common available antiepileptic medications like phenytoin, phenobarbitone, ethosuximide, sodium valproate, and carbamazepine as poly or mono therapy regimens ordinarily associated with hepatotoxicity[16, 17]. Gabapentin administration also found to have negative effects on the healing of the fractures particularly in regard to the biomechanical as well as histological progression the in rat model [18].
Gabapentin has various chemical properties, it is 1-(amino methyl) cyclohexane acetic acid, its molecular formula is C9H17NO2, structurally analogous to gamma aminobutyric acid (GABA) with white crystalline substance[19], has bitter-tasting, considered as a freely water-soluble in both basic and acidic aqueous solutions. The assay of this drug was done in both urine and plasma using the HPLC and gas chromatography PH is very important for the activity and stability of gabapentin, for example formation of small amount of lactam may exist in the aqueous solutions but this can be decreased and may be neglected at the pH 6.0[20].
The available form of gabapentin is the oral preparations, and the absorption is slow and takes place in the small intestine via facilitated transport and diffusion. After oral administration, transport of gabapentin from the digestive canal is facilitated by its binding to a special receptor and the way is a saturable L-amino acid transport mechanism, so the absorption is dose-dependent[21]. The oral bioavailability of the absorbed gabapentin is inversely varying with the value of dose, for example after the administration of a single dose of 600 or 300 mg, the bioavailability will be about 40% and 60%, respectively[22]. After absorption, the circulation of the GPN occurs mostly unbounded, will not metabolized in the plasma and excreted or eliminated unchanged by the kidneys[2, 23]. Gabapentin half-life is correlated to the creatinine clearance and is about 5-7 hours, so in patients with renal failure excretion is decreased[24].

Aim of the study

To investigate the probable histological changes accompanied with the use of gabapentin.

Materials and Methods

Eight adult's white male rats were brought from the animal house of the college of science-university of Babylon to the lab of biology in the college of pharmacy, animals were fed on pellets and were left for two weeks for adaptation. The dose used in this research is determined according to the usual oral dose for human, and the detection depends on the body weight take into consideration the metabolic activity. After adaptation time, five animals were treated orally with 300 mg/day of gabapentin (actavis company) by using oral tube for gavage method, while three animals were used as a control group and were given a DW.
Treatment period was one month, then animals were euthanized (under anesthesia) for the histological study.

Results and Discussion

The experimental rat exposed to gabapentin looked apparently normal with no behavioral abnormalities of any kind , the histopathology side of the liver parenchymal cell shows no abnormalities but a few lymphocytes infiltration, while kidney, pancreas and spleen were found to be normal in all individuals of the experimental rats in compare with control group. These results were shown in the figures (1, 2, 3, 4, 5, 6, 7, 8).

Up to data published on the effect of administration of gabapentin on hepatic tissue in adult rat, the result showed that gabapentin has no significant effect.

In contrast other studies shows that the long term treatment with old or new anti-epileptic drug affect liver function from transient state to fatal liver damage[16, 25], but when considered gabapentin such an effect is quit less and no report of death or fatal liver damage . A recent study with low of gabapentin _ antidepressant combination with opioids was effective in managing neuropathic cancer pain without sever adverse effect[26].

Another studies found that the effect of gabapentin is dose related [27, 28]. According to these studies, the activity of liver enzymes with 20 mg/kg of gabapentin has no significant differences from that of the control group, while the levels of alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, total and direct bilirubin were significantly increased with the dose 100 mg/kg.

Gabapentin also found to affect the histology of the kidney of fetuses by the presence of vacuolar degeneration and dilatation in the epithelium of the convoluted tubules accompanied by a hemorrhage among the tubules, the glomerular atrophy, edematous effects, marked thickening of the basement membranes of the glomeruli, numerous changes in the convoluted tubules including partial destruction of the apical brush border microvilli and obvious thickening of the basal lamina of the lining cells. At the level of immunohistochemistry, other effects were present such as the expression of decrease of Bcl-2 in the epithelial cell's cytoplasm of convoluted tubule and the increase of Caspase-3 expression[29].

Case study researches emphasized that doctors should be careful in the use of gabapentin in some patients with acute illness, particularly those with renal impairments[30, 31].

In regard to the pancreas, it was found that gabapentin didn't affect the weight of this organ, the acinar cells proliferation and the ductal cell in compare with the control group, but gabapentin may have a significant effects on the expression of some oncogenes in compare with the control group[32].

The present study concludes that exposure of rat to therapeutic dose of gabapentin result in no change in liver tissue, so it can be drug of choice for patient with neuropathic pain or epilepsy.

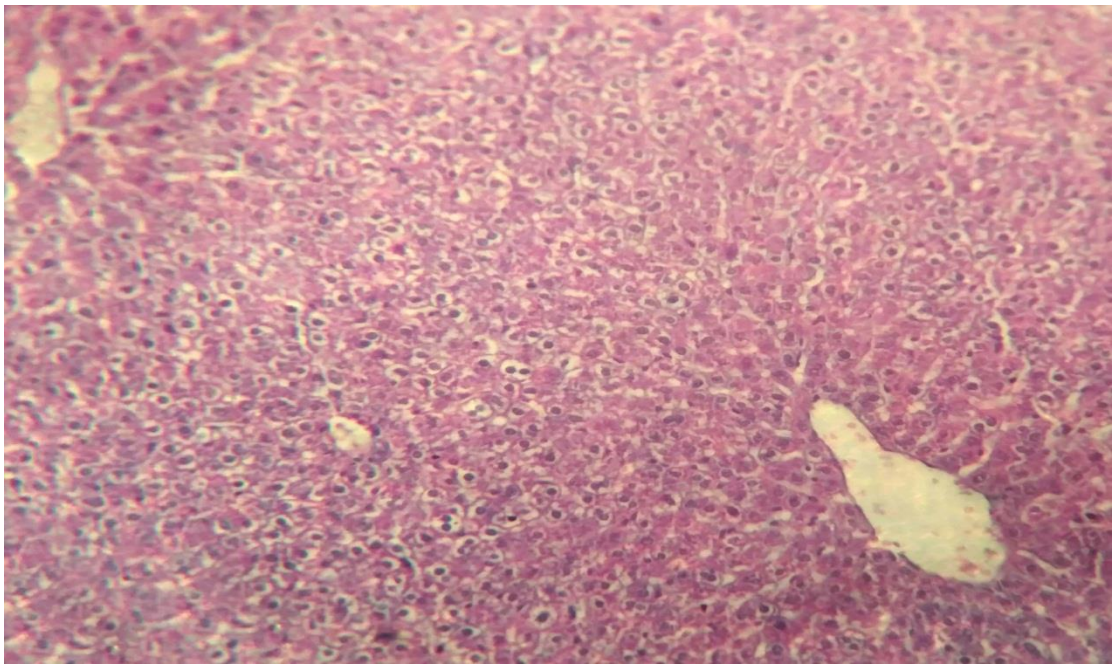

Figure 1: Cross histological section of the liver of normal rat (control group) showing normal histology. 200x

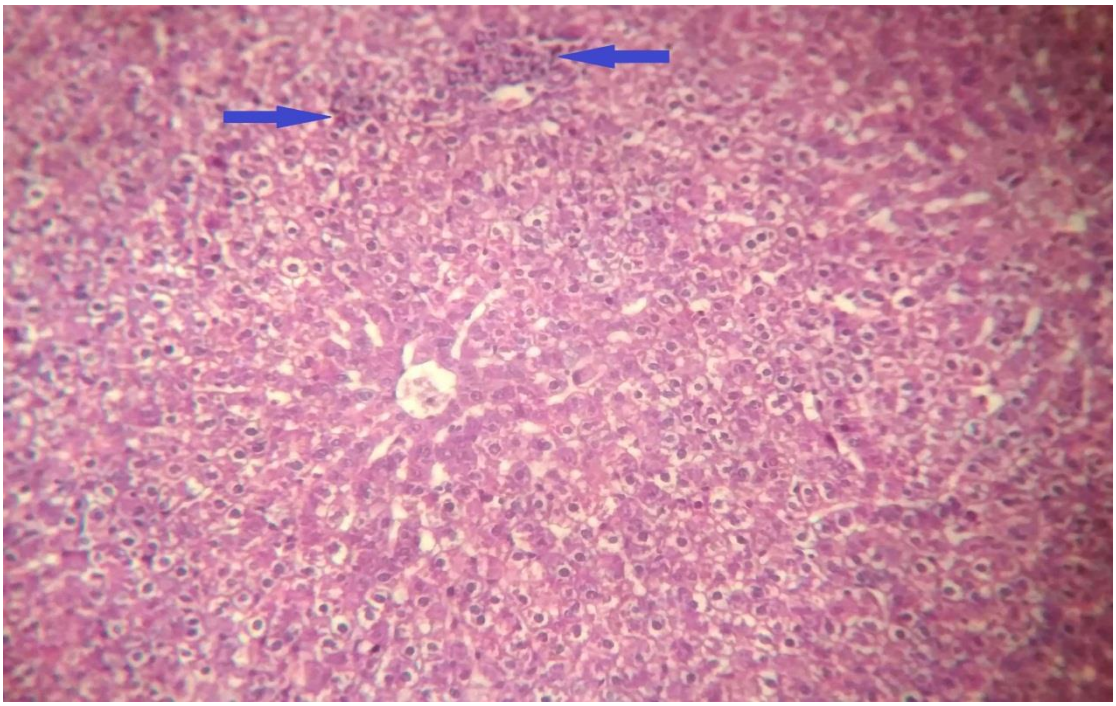

Figure 2: Cross histological section of the liver of rat treated with 300 mg/day of gabapentin, showing the presence of a few lymphocyte infiltration (blue arrows). 200x

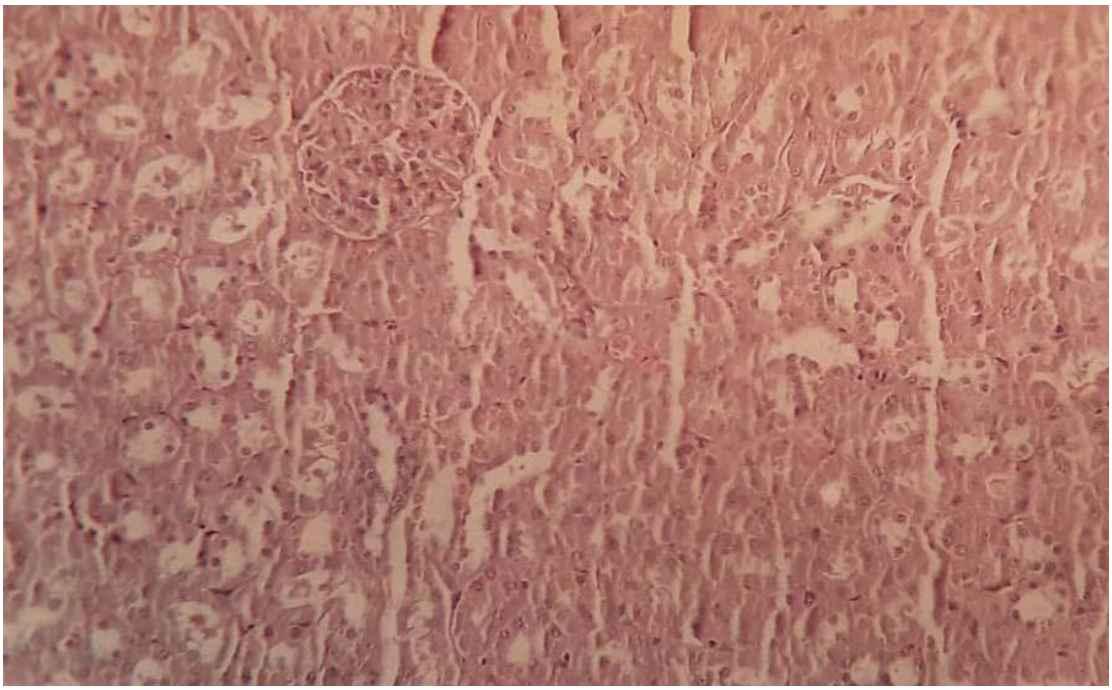

Figure 3: Cross histological section of the kidney of normal rat (control group) showing normal histology. 200x

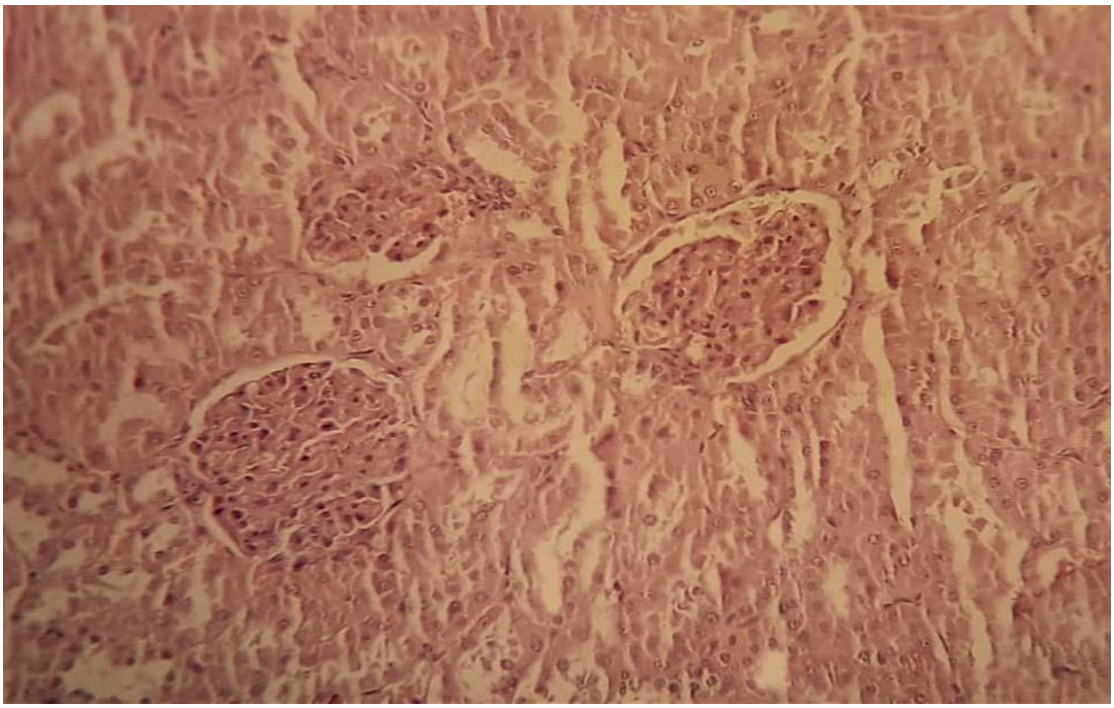

Figure 4: Cross histological section of kidney of rat treated with 300 mg/day of gabapentin, showing normal histology. 200x

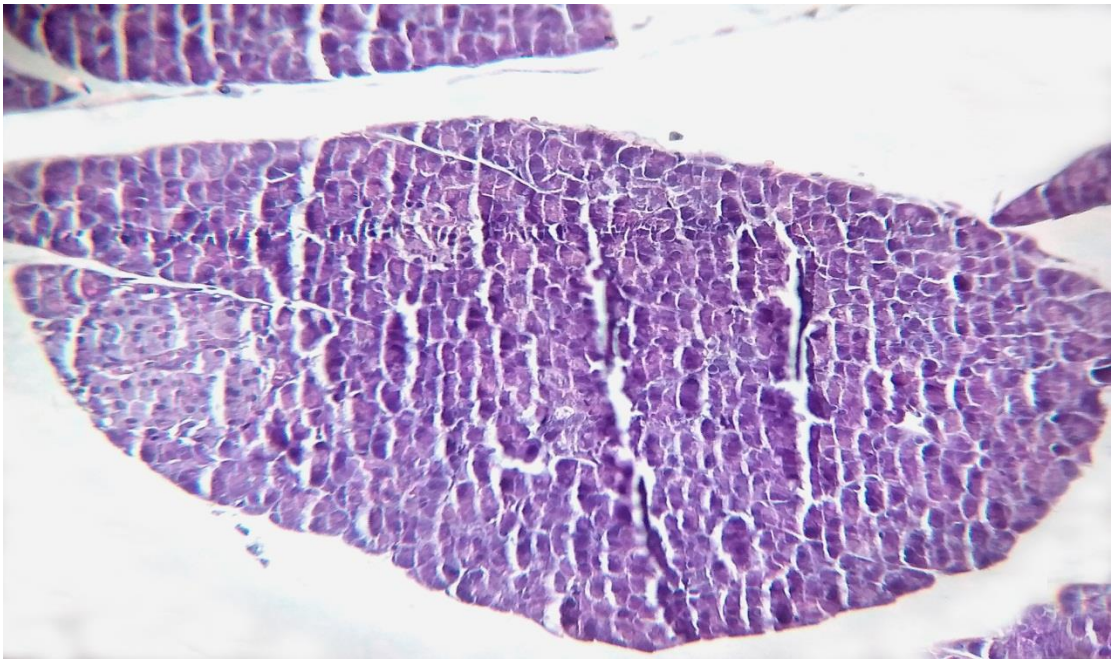

Figure 5: Cross histological section of the pancreas of normal rat (control group) showing normal histology. 200x

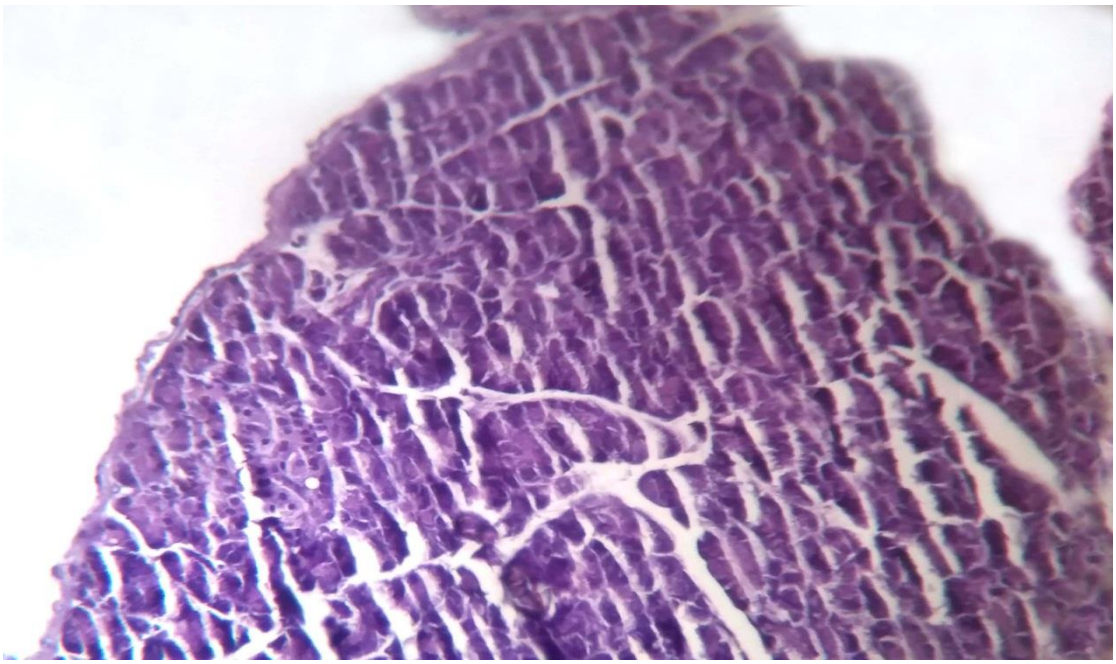

Figure 6: Cross histological section of pancreas of rat treated with 300 mg/day of gabapentin, showing normal histology. 200x

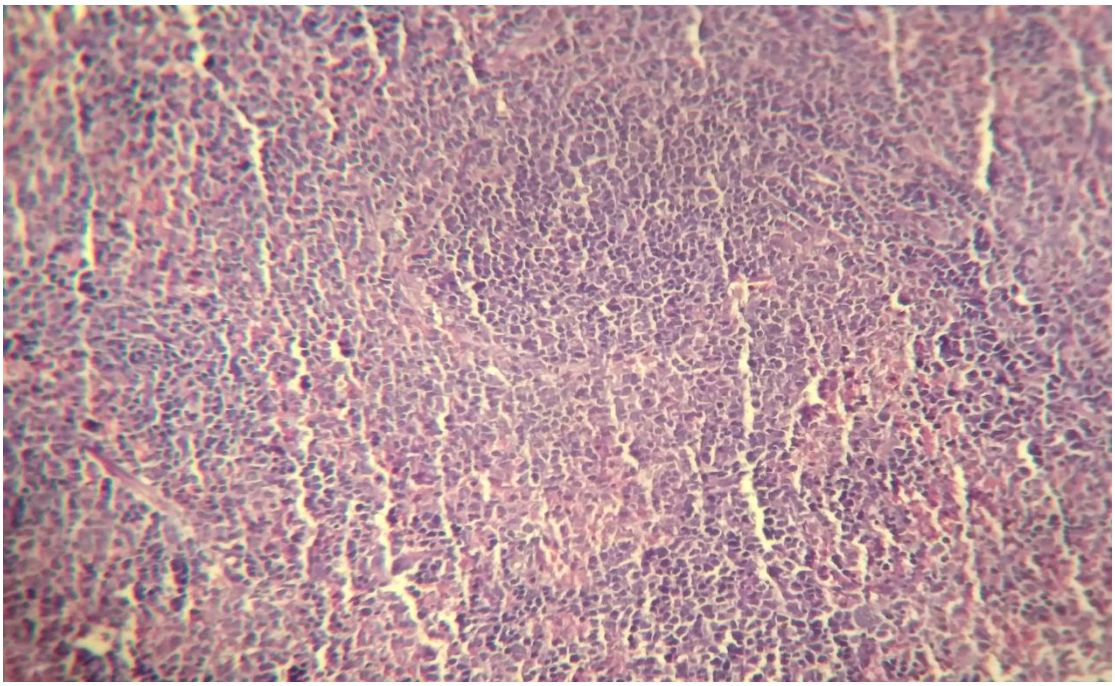

Figure 7: Cross histological section of the spleen of normal rat (control group) showing normal histology. 200x

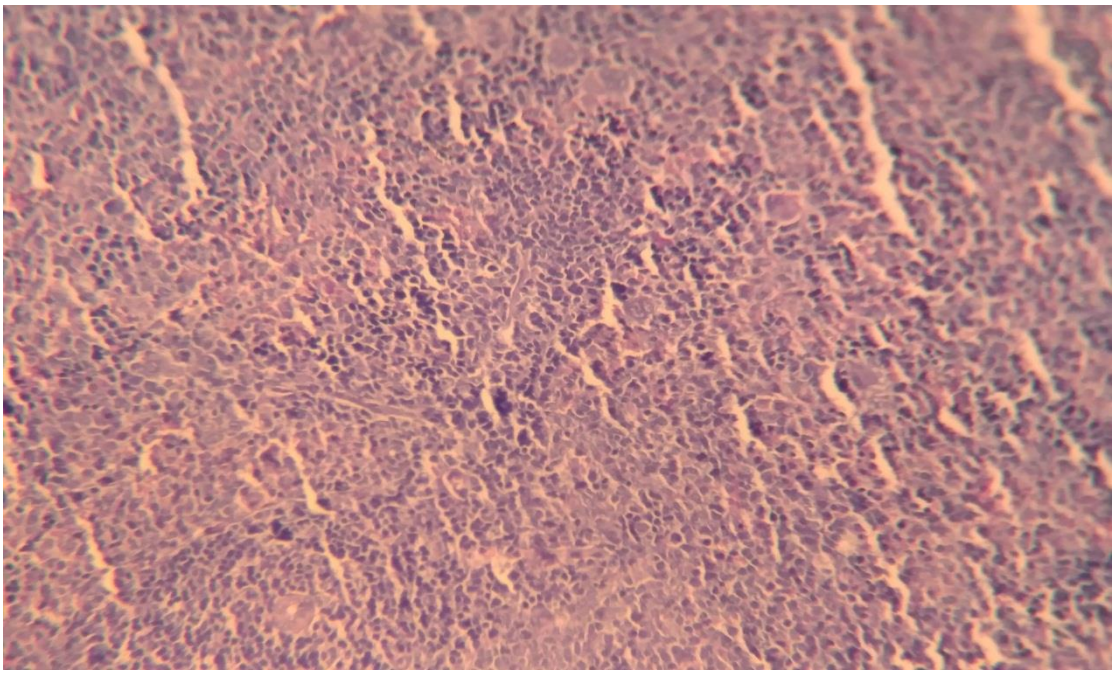

Figure 8: Cross histological section of spleen of rat treated with 300 mg/day of gabapentin, showing normal histology. 200x

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