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A histopathological study of nephrotoxicity, hepatoxicity or testicular toxicity: Which one is the first observation as side effect of Cisplatin-induced toxicity in animal model?

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ABSTRACT

Background: Cisplatin (CP) is widely used in clinic to treat the solid tumors. However, CP is associated with some major side effects including nephrotoxicity, hepatoxicity, and testicular toxicity.
Objectives: To found, which of the toxicities is the first side effect of CP.
Materials and Methods: we conducted a pilot research on 12 adult male Wistar rats.
Results: One week after CP administration, the induced toxicity was observed clearly in kidney tissue. The only abnormality that observed in testis tissue was very small degree of hyaline casts. However, no damage and other abnormality were detected in the liver tissue.
Conclusions: According to these findings, in clinic, first special attention must be made on kidneys during chemotherapy with CP. However, the duration of experiment is suggested to be extended to obtain hepatoxicity or testicular toxicity model in experimental animal in laboratories. Moreover, different dose of CP should be used to study the first side effect in animal model.

Brief Report

Implication for health policy/practice/research/medical education:
Cisplatin (CP) is widely used in clinic to treat the solid tumors. However, CP is associated with various major side effects including nephrotoxicity, hepatoxicity, and testicular toxicity. In clinic, first special attention must be made on kidneys during chemotherapy with CP.

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1. Background

Cisplatin (CP) is widely used in clinic to treat the solid tumors (1-3). However, CP is associated with some major side effects including nephrotoxicity (4, 5), hepatoxicity (6-8) and testicular toxicity (9, 10) .

The side effects of CP treatment on testis are include germ cell apoptosis (11-13), long–lasting azoospermia and testicular atrophy (14), and dysfunction of any type of cells in testis of animal (15). While experimental data indicated that CP impairs rat liver mitochondrial functions and promote apoptosis (16, 17). CP-induced nephrotoxicity is accompanied with, tubular cell apoptosis, tubular dilatation, cast formation, debris and necrotic materials in the tubular lumens (18-21).

2. Objectives

In our research on CP-induced nephrotoxicity in animals' model, we found that the occurrence of nephrotoxicity was the first side effect in animals treated with CP,, and therefore they are reported here.

3. Methods and Materials

This pilot research was performed on 12 adult male (180-220 gr) Wistar rats. The rats were housed at a temperature of 23–25°C. They had free access to water and rat chow, and they were acclimatized to this diet for at least 1 week prior to experiment. The experimental procedures were approved in advance by the Isfahan University Medical Sciences Ethics Committee.

The animals were randomly divided into two experimental groups. The groups 1 (n=6) received a single dose of CP (6 mg/kg), while the group 2 (n=6) had vehicle instead of CP. The CP (cis-Diammineplatinum (II) dichloride, code P4394), was purchased from Sigma. All the animals sacrificed one week post CP injection, and their kidney, liver and testis were removed and fixed in 10% neutral formalin solution and were embedded in paraffin for histopathological staining. The hematoxylin and eosin stain were applied to examine the tissues damages. Some abnormalities such as, tubular dilation, cast, debris and necrotic materials in the tubular lumen and lymphocytes in interstitial tissue area, leyding cell hyperplasia, inflammation, atrophy, and maturation for the testis tissue, and cholestasis, steatosis, or other abnormalities for liver tissue were considered as damages by three independent pathologists.

4. Results

One week after CP administration, the induced toxicity was observed clearly in kidney tissue. More than 50% of the kidney tissue was disturbed. However, the only abnormality that observed in testis tissue was very small degree of hyaline cast. However, no damage and other abnormality were detected in the liver tissue (figure 1).

5. Conclusions

According to these findings, in clinic, first special attention must be made on kidneys during chemotherapy with CP. However, the duration of experiment is suggested to be extended to obtain hepatoxicity or testicular toxicity model in experimental animal in laboratories. Moreover, different dose of CP should be used to study the first side effect in animal model.

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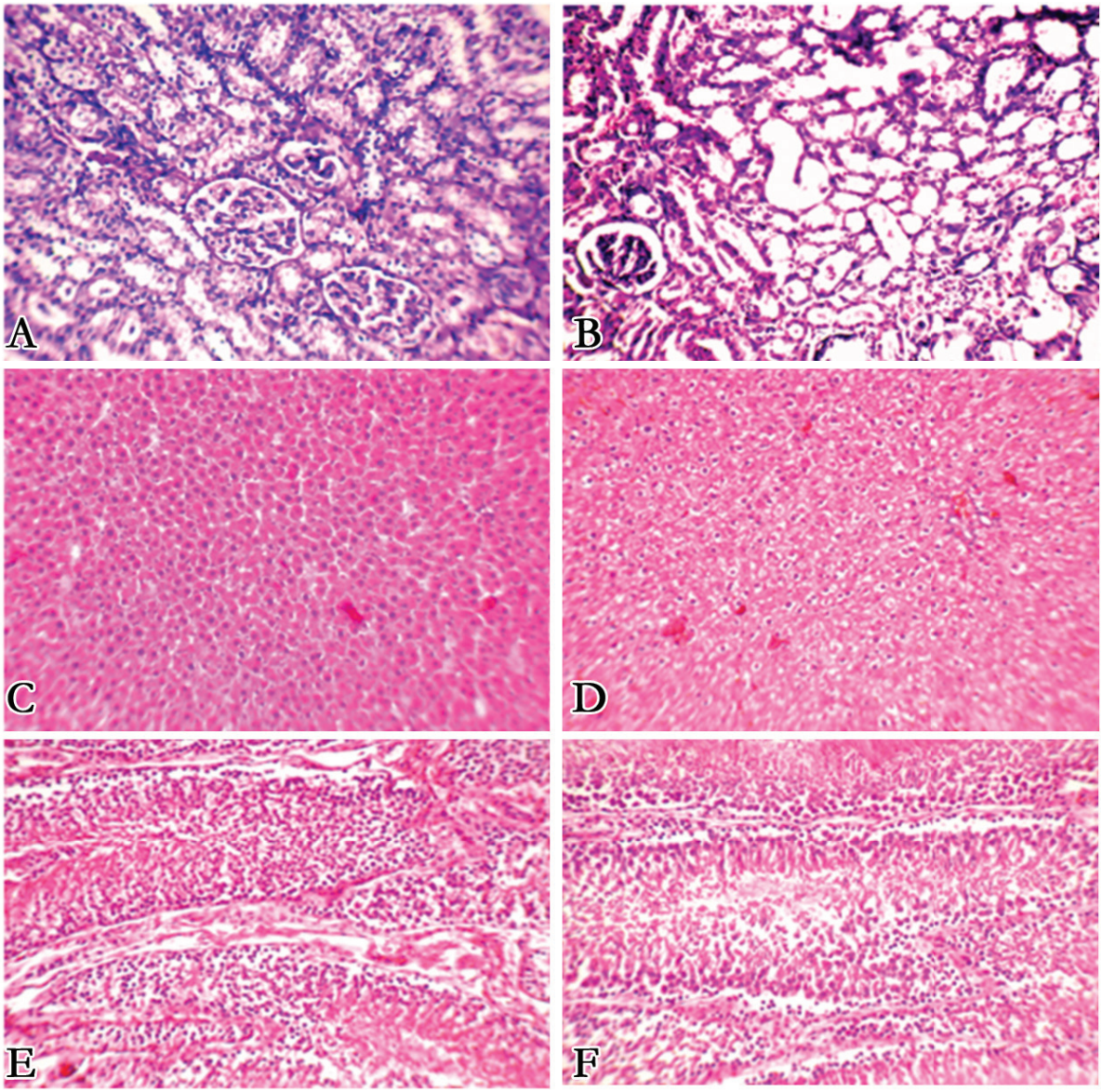

Figure 1. The images of A, C and E corresponds to normal kidney, liver and testis tissues in normal animal group. B, D and F are the images of kidney, liver and testis tissues from the CP treated rats. The severe kidney tissue damage was observed in CP treated rats (B), while no serious damage were detected in liver and testis tissues in CP treated animals. (x100)

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References

1. Tsimberidou AM, Moulder S, Fu S, Wen S, Naing A, Bedikian AY, et al. Phase I clinical trial of hepatic arterial infusion of cisplatin in combination with intravenous liposomal doxorubicin in patients with advanced cancer and dominant liver involvement. Cancer Chemother Pharmacol.. 2010;66(6):1087-93.

2. Bergs JW, Franken NA, Haveman J, Geijsen ED, Crezee J, van Bree C. Hyperthermia, cisplatin and radiation trimodality treatment: a promising cancer treatment? A review from preclinical studies to clinical application. Int J Hyperthermia.. 2007;23(4):329-41.

3. Fujiyama J, Nakase Y, Osaki K, Sakakura C, Yamagishi H, Hagiwara A. Cisplatin incorporated in microspheres: development and fundamental studies for its clinical application. J Control Release.. 2003;89(3):397-408.

4. Stewart DJ, Dulberg CS, Mikhael NZ, Redmond MD,

Montpetit VA, Goel R. Association of cisplatin nephrotoxicity with patient characteristics and cisplatin administration methods. Cancer Chemother Pharmacol.. 1997;40(4):293-308.
5. Saad AA, Youssef MI, El-Shennawy LK. Cisplatin induced damage in kidney genomic DNA and nephrotoxicity in male rats: the protective effect of grape seed proanthocyanidin extract. Food Chem Toxicol.. 2009;47(7):1499-506.
6. Liao Y, Lu X, Lu C, Li G, Jin Y, Tang H. Selection of agents for prevention of cisplatin-induced hepatotoxicity. Pharmacol Res.. 2008;57(2):125-31.
7. Cersosimo RJ. Hepatotoxicity associated with cisplatin chemotherapy. Ann Pharmacother.. 1993;27(4):438-41.
8. Kohn S, Fradis M, Robinson E, Iancu TC. Hepatotoxicity of combined treatment with cisplatin and gentamicin in the guinea pig. Ultrastruct Pathol.. 2005;29(2):129-37.
9. Atessahin A, Sahna E, Turk G, Ceribasi AO, Yilmaz S, Yuce A, et al. Chemoprotective effect of melatonin against cisplatin-induced testicular toxicity in rats. J Pineal Res.. 2006;41(1):21-7.
10. Strumberg D, Brugge S, Korn MW, Koeppen S, Ranft J, Scheiber G, et al. Evaluation of long-term toxicity in patients after cisplatin-based chemotherapy for non-seminomatous testicular cancer. Ann Oncol.. 2002;13(2):229-36.
11. Cherry SM, Hunt PA, Hassold TJ. Cisplatin disrupts mammalian spermatogenesis, but does not affect recombination or chromosome segregation. Mutat Res.. 2004;564(2):115-28.
12. Zhang X, Yamamoto N, Soramoto S, Takenaka I. Cisplatin-induced germ cell apoptosis in mouse testes. Arch Androl.. 2001;46(1):43-9.
13. Huddart RA, Titley J, Robertson D, Williams GT, Horwich A, Cooper CS. Programmed cell death in response to chemotherapeutic agents in human germ cell tumour lines. Eur J Cancer.. 1995;31A(5):739-46.
14. Pont J, Albrecht W. Fertility after chemotherapy for testicular germ cell cancer. Fertil Steril.. 1997;68(1):1-5.
15. Sawhney P, Giammona CJ, Meistrich ML, Richburg JH. Cisplatin-induced long-term failure of spermatogenesis in adult C57/Bl/6J mice. J Androl.. 2005;26(1):136-45.
16. Martins NM, Santos NA, Curti C, Bianchi ML, Santos AC. Cisplatin induces mitochondrial oxidative stress with resultant energetic metabolism impairment, membrane rigidification and apoptosis in rat liver. J Appl Toxicol.. 2008;28(3):337-44.
17. Custodio JB, Cardoso CM, Santos MS, Almeida LM, Vicente JA, Fernandes MA. Cisplatin impairs rat liver mitochondrial functions by inducing changes on membrane ion permeability: prevention by thiol group protecting agents. Toxicology.. 2009;259(1-2):18-24.
18. Nematbakhsh M, Ashrafi F, Safari T, Talebi A, Nasri H, Mortazavi M, et al. Administration of vitamin E and losartan as prophylaxes in cisplatin-induced nephrotoxicity model in rats. J Nephrol.. 2012 ;25(3):410-7.
19. Liu XH, Li J, Li QX, Ai YX, Zhang L. Protective effects of ligustrazine on cisplatin-induced oxidative stress, apoptosis and nephrotoxicity in rats. Environ Toxicol Pharmacol.. 2008;26(1):49-55.
20. Santos NA, Bezerra CS, Martins NM, Curti C, Bianchi ML, Santos AC. Hydroxyl radical scavenger ameliorates cisplatin-induced nephrotoxicity by preventing oxidative stress, redox state unbalance, impairment of energetic metabolism and apoptosis in rat kidney mitochondria. Cancer Chemother Pharmacol.. 2008;61(1):145-55.
21. Santos NA, Catao CS, Martins NM, Curti C, Bianchi ML, Santos AC. Cisplatin-induced nephrotoxicity is associated with oxidative stress, redox state unbalance, impairment of energetic metabolism and apoptosis in rat kidney mitochondria. Arch Toxicol.. 2007;81(7):495-504.