Research Paper

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Prostatic Stromal Hyperplasia after Doxorubicin Treatment in the Albino Rat

Zoology

KEYWORDS : Prostate, albino rat, stromal hyperplasia, benign carcinoma

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ABSTRACT

The prostate is of the great clinical importance because it is a frequent site of infection and benign and malignant growth. Although glandular and stromal proliferation of prostate is very common, neoplastic proliferations of prostatic stroma are distinctly uncommon. The current study reported the effect of an anticarcinogenic drug, Doxorubicin (1mg/Kg BW/30days) and (2mg/Kg BW/30days) on the prostate gland of male albino rat. The prostatic stromal hyperplasia was characterised by the presence of bizarre giant cells with vacuolated nuclei and frequent multinucleation. The chromatin was smudged rather than hyperchromatic. Nucleoli were inconspicuous or absent owing in part to the nuclear smudging. Inspite of many bizarre, pleomorphic nuclei, mitosis were inconspicuous or occasional. Many nuclei showed nuclear vacuolation, giving a bubbly appearance to it. Some nuclei showed eosinophilic inclusion probably cytoplasmic invaginations. In some foci hyalinised stroma was seen while other places showed loose oedematous stroma suggestive of degenerative changes. Similarly the blood capillaries from the 2mg/Kg BW/30days group exhibited an increase in cellularity of blood vessel wall. All the hyperplastic effects were dose dependent, being more conspicuous in 2mg/Kg BW/30days. From our observations it may be interpreted that these atypical features to be degenerative rather than neoplastic. Recognition of such benign entity has important therapeutic and prognostic implications.

Introduction

Prostate stromal hyperplasia with atypia is a benign finding associated with infrequent recurrence, similar to and usually coexisting with typical nodular hyperplasia; it lacks evidence of stromal overgrowth or transformation with follow up and has been only reported in the human either as disease or after post-irradiation (Attah and Powell, 1977; Leong et al. 1988; Tetu et al. 1988; Young et al. 1988; Eble and Tejada, 1991; Shapiro et al. 1992; Wang and Bostwick, 1997; Herawi and Epstein, 2006; Hossain et al. 2007, 2008; Iczkowski, 2009) however, reports on experimental basis are few and scanty (Mori et al. 2009). Substantial and characteristic changes in the microscopic appearance of prostatic stroma have been noted following an anticancer drug Doxorubicin administration which are reported in the present paper using rat as a model. Doxorubicin (14-Hidroxydaunorubicin) is an anthracyclic antibiotic drug widely used in the treatment of a variety of cancers (Di Marco and Arcamone, 1975; Schwartz, 1976). Doxorubicin has multiple mechanisms of action, including its interaction with the enzyme topoisomerase II, metal ion chelation and free radical generation (Xu et al. 2005). More recently doxorubicin was found to reduce the viability of cancer cells via RNA damage (Fimognari et al. 2008). These atypical changes in prostatic fibromuscular stroma could be related to atypical changes in the connective tissue stroma of the female breast, cervix, vagina and bladder (Young and Scully, 1987; Wick et al. 1988; Pitt et al. 1993). The perusal of literature revealed that benign soft tissue tumours of the prostate are rare (Beltran, 1999) and hence recognition of this benign entity in the rat prostate after Doxorubicin treatment may have important therapeutic and prognostic implications (Hossain et al. 2007, 2008).

MATERIAL AND METHODS

Chemicals

Doxorubicin hydrochloride (Fresenius Kabi Oncology Limited, Solan, India).

Animals and treatment

The Wistar rat, *Rattus norvegicus* weighing between 250 to 300gms were selected. For the present study, animals were obtained from Department of Biochemistry, RTM Nagpur University Nagpur. After a week of acclimatization to laboratory condition, Doxorubicin was administered via disposable syringe intraperitoneally. The control animals received same amount of saline (Tables - 1 and 2).

Histological assessment

The animals were sacrificed using chloroform 24 hours after the last day of each experiment. Immediately ventral prostate was excised and fixed in Bouin's solution, dehydrated in ethanol and embedded in paraffin wax. The sections cut in 5 µm were stained with haematoxylin and eosin.

Table - : Experimental Design for Doxorubicin low dose treatment

Number of animals and sex	Treatment	Dose mg/Kg BW	Route	Duration
6 males (Experimental)	Doxorubicin	1mg daily	I.P.	30 days
6 males (control)	Saline	E.V.	I.P.	30 days

Table 2-: Experimental Design for Doxorubicin high dose treatment

Number of animals and sex	Treatment	Dose mg/Kg BW	Route	Duration
6 males (Experimental)	Doxorubicin	2 mg daily	I.P.	30 days
6 males (control)	Saline	E.V.	I.P.	30 days

Abbreviations : E.V. = Equal volume, I.P. = Intraperitoneal, B.W. = Body weight

Results:-

Vehicle-treated controls

Out of the three lobes, dorsal, lateral and ventral, ventral prostate has been used for the present study. These lobes are connected to the urethra by fascia and a series of ducts. The prostate is a compact compound tubular gland lying in the close approximation to the bladder. The gland have a thin membranous capsule. The glandular substance was spongy. The prostate showed two clearly marked regions, a cranial peripheral unit of secreting tubules and a caudal ventral unit of collecting tubules. From the capsule thin trabeculae of elastic stroma containing randomly oriented smooth muscle bundles extended inward and formed the boundaries of the lobules. The lobules were formed of a closely packed network of glandular lobules or acini. Flat squamous epithelium or pseudostratified comprising tall columnar cells and basal cells lined the large distended acini with dense secretory material. These large acini were isolated by moderate amount of fibromuscular tissue which consisted of few typical spindle-shaped mesenchymal cells with large hyperchromatic nuclei (figs. 1 and 2).

Chronic low dose treatment (1mg/KgBW/ 30days)

Following this treatment there was an extensive shrinkage of prostatic acini but remarkable development of prostatic epithelium lining most of the acini, such overgrowth may be the

papillary type of carcinoma. The inter - acinal spaces were occupied by extensively grown mixoid and hypercellular stroma (fig.3). Variable number of large bizarre atypical cells, nuclear pleomorphism without mitotic figures, vacuolated nucleoli with a bubbly appearance, smudged chromatin, inconspicuous nucleoli were found embedded in the hyalinized stroma. Similarly enlarged hyperchromatic sarcomatoid nuclei were noted in the vicinity. The hyalinized stroma was hypercellular whereas mixoid stroma was hypocellular (figs. 3, 4, 5). These atypical cells mostly displayed degenerative character of the nuclear changes including, absent to negligible mitotic rate (figs.3, 4, 5 and 6). The blood vessels showed inflammatory changes such as perivascular fibrosis (fig.6).

Chronic high dose treatment (2mg/KgBW/ 30days)

An increment in the dose caused hypercellularity of the atypical cells in the stroma, however, when compared with the previous dose the growth of mixoid and hyalinized stroma was less, but the papillary type of acinal carcinoma was more prominent (fig.7). The atypical cells were uncircumscribed, ill-defined, with distinctive nuclear features, inconspicuous nucleoli or absent owing in part to nuclear smudging, with moderate amount of eosinophilic cytoplasm (fig. 8). These degenerative changes were more enhanced by the clumping of chromatin material into syncytium formation (fig. 9). When compared to the previous dose profuse infiltration of atypical cells into the benign prostatic acinus was atypical. Mostly spindle-shaped cells with scanty, pale, eosinophilic cytoplasm and ill-defined margins from the hyalinised area were found to penetrate the basement membrane of papillary epithelium (fig.10 and 11). The notable feature when compared to the previous dose was more degenerative characters of the nuclear changes accompanied by inflammatory changes in the blood vessels. The invariably large ectatic vessels with hyalinised, thick wall accompanied by a variable number of lymphocytes, plasma cells and mast cells were a common sight (fig.12).

Discussion

The accessory sex glands are essential for the maintenance of fertility in different species (Chow and W.S.O. 1989). The prostate an accessory gland is a complex gland formed by three pairs of lobes: the ventral, dorsal and lateral lobes distributed around the male urethera in rodents (Jesik et al., 1982). The prostate is also of the great clinical importance because it is a frequent site of infection and benign and malignant growth. Although glandular and stromal proliferation of prostate is very common, neoplastic proliferations of prostatic stroma are distinctly uncommon. The current study reported the effect of an anticarcinogenic drug, Doxorubicin (1mg/Kg BW/30days) and (2mg/Kg BW/30days) on the prostate gland of male albino rat particularly on ventral lobe.

In our studies the prostatic stromal hyperplasia was found to be dose and duration dependent thus the changes were more enhanced in the 2mg/KgBW/30 days Group. The benign prostatic hyperplasia observed in the present study were reactive and degenerative rather than neoplastic and such changes are coharant to the stromal changes from cervix, vagina, vulva, bladder, breast as well as to the observation of Young and Scully, 1987; Young, 1988; Leong et al. 1988; Shapiro et al. 1992; Wick et al. 1988; Pitt et al. 1993; Attah and Powell, 1977; Wang and Bostwick, 1997; Eble and Tejade, 1991; Herowi and Epstein, 2006; Hossain et al. 2008; Iczkowski, 2009; Mori et al. 2009.

Conclusion

From our observations it may be interpreted that these atypical features were degenerative rather than neoplastic. Recognition of such benign entity have important therapeutic and prognostic implications.

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