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Original Article

Thymus Hypertrophy in Orchidectomized Rats: An Immunohistochemical Study

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ABSTRACT

Background: The thymus is considered to be a primary sex hormone-responsive organ, which plays an important role in maintaining a competent immune system.

Aim of the Work: This research was conducted to study the orchidectomy-induced changes in the lymphocytic as well as the non-lymphocytic contents of the rat thymus using histological, immunohistochemical and histometrical methods.

Material and Methods: Twenty male adult rats were randomly divided into two groups (control and orchidectomized). The animals were housed in cages with softwood granules as bedding. They had free access to standard diet and drinking water. Animals were sacrificed by cervical dislocation after four weeks of orchidectomy. The entire thymuses were dissected out, plot dried and weighed. Organ weights were expressed as absolute and relative weight (g/100g body weight). Five-µm sections were stained using Weigert's haematoxylin and van Gieson's stains for fibrous tissue, Periodic acid Schiff (PAS) for glycoproteins, methyl green-pyronin for plasma cells, Unna stain for mast cells and S-100 immunoperoxidase stain for interdigitating cells.

Results: In orchidectomized rats the absolute and relative thymic weight, the mean thickness of the cortex and the cortex/medullary ratio were significantly increased in comparison to the control rats. Using image analysis and color subtraction, the area% of the interdigitating cells in cortex and medulla was calculated, there was a significant decrease in the area% of the interdigitating cells both in the cortex and the medulla of the orchidectomized rats versus the control.

Conclusions: Thymus is an androgen – responsive tissue. The extract role of interdigitating cells in age induced thymic atrophy remain to be elucidated.

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Key Words: Orchidectomy, rats, thymus, immuno-histochemistry

INTRODUCTION

Steroids can exert a profound influence over the immune response. In general, Estrogen has immunostimulatory effect *(Ansar Ahmed, et al. 1989)*, while androgen has immunosuppressive effect *(Schuurs and Verheul, 1990)*. Thus, females are more susceptible to autoimmune diseases like systemic lupus erythromatosis (SLE) and Hashimato thyroiditis, while men are significantly less affected by all autoimmune diseases. On the other hand, ablation of sex hormone function or production constitutes a common therapeutic strategy for the treatment of hormone responsive tumors such as prostate and breast cancer. Moreover, previous evidence suggests that androgen ablation therapy of prostate cancer patients induces elevations in circulating lymphocytes; a change which is associated with a more favorable prognosis *(Oliver and Gallagher, 1995)*.

The thymus is a bilobed elongated lymphoepithelial organ located in the superior mediastinum that ensures T-cell differentiation and maturation *(Gartner and Hiatt, 1997)*. The mammalian thymus consists of two distinct lobes connected by a connective tissue isthmus. A thin connective tissue capsule surrounds each lobe and, in most species, gives rise to septae, that partially subdivide the thymus into interconnecting lobules of variable size and orientation *(Haley, 2003)*. It undergoes age-related (chronic, physiological) involution in the course of normal ontogenetic development *(Haynes, 2000)*. In addition, it can undergo an acute

(age-independent) regression, defined as spontaneous transient involution. This process is induced by either exogenous or endogenous factors, such as stress and malnutrition, or by pathological events, including some infections *(Turke, 1997)*.

Several studies have suggested that thymus is a primary sex hormone-responsive organ *(Verthelyi, 2001; Yao and Hou, 2004)*. It is confirmed by the fact that T-cell production by the thymus is maximal during young age and then decreases significantly after the onset of puberty under the influence of sex hormones. In addition, it has been shown that the thymus involutes extensively during human and animal pregnancy *(Clark and Kendall, 1994)*. This involution is partially due to massive cortical thymocytes death and extensive phagocytosis of immature cortical thymocytes *(Kendall, 1990)*.

Although the histological changes that occurred in the thymus gland after gonadectomy and after administration of various sex steroids (testosterone, estrogen, and progesterone) have been studied before *(Wei, et al. 2001; Oner and Ozan, 2002)*, however, little information is available about structural changes that occur in the non-lymphoid component of the thymus that play an important role in T-cell development. The aim of this work is to study the histological, immunohistological and histometrical changes of the adult male rat thymus following orchidectomy.

MATERIAL AND METHODS

Animals used: Twenty male albino rats more than nine months old were used in this study. The animals were divided randomly into two groups (n = 10). Group I, sham control group. Group II, orchidectomized (castrated) rats. The animals were housed in cages with softwood granules as bedding and had free access to standard diet and drinking water.

Orchidectomy: Castration was performed using standard method of *Azad et al. (1998)*. Male rats were anesthetized with intraperitoneal injection with 10% chloral hydrate (300 mg/kg). The scrotal sac was cleaned with antiseptic and an incision of approximately 2 cm was made midsagittally at the scrotal septum. The spermatic cords were dissected, tied and cut. The testes were carefully removed from the scrotal sac and the incision was then sutured by absorbable suture. In sham operations, the scrotal incisions were immediately sutured and the gonadal system was not manipulated. Animals were returned to the cages when they recovered from the anesthesia and were able to eat and drink.

Tissue processing: All animals were sacrificed by cervical dislocation after four weeks of castration. The entire thymuses were dissected out, plot dried and weighed. Organ weights were expressed as absolute and relative weight (g/100g body weight). The entire thymuses were then kept in bouin's fixative for at least three days. Tissues were dehydrated in ascending concentrations of ethyl alcohol, cleared in xylene and embedded in paraffin. Five-micrometer-thick sections were cut and stained with Weigert's haematoxylin and van Gieson's stains for the fibrous tissue content of the thymus. Periodic acid Schiff (P.A.S) for glycoproteins. Methyl green-pyronin stain for plasma cells. Unna stain for mast cells. S-100 immunoperoxidase stain for interdigitating cells.

Morphometry: To quantitatively evaluate cortex/medullary ratio of the thymus, all functional lobules with an outer cortex and inner medulla were measured using ocular micrometer. In order to avoid errors resulting from tangential cuts that can occur within any given lobule, all lobules were examined and an overall ratio was determined.

Imaging: Tissue sections were examined and photographed using an Olympus microscope. Images were scanned using Acer 640P scanner, saved as RGB color TIFF files and used for the histomorphometrical analysis-using image processing computer software NIH ImageJ (http://rsb.info.nih.gov/ij/Java 1.5.1_06).

Image analysis: Images were calibrated against a calibrated stored image of a known value photographed with the same magnification as the non-calibrated images. The area% occupied by the intrerdigitating cells in cortex and medulla were calculated in a standard measuring frame using color subtraction. The color subtraction sequence removed the non-peroxidase background colors by replacing them with white. The area% occupied by the interdigitating cells was delineated, thresholded and calculated both in the cortex and in the medulla.

Statistical Analysis: Data were expressed as means ± SD. Differences between groups were determined using independent sample student t-

test after testing for normal distribution. The cortex and medulla thickness were log transformed to achieve normal distribution and justify the use of student t-test in comparison. Significant differences were attributed with $P \leq 0.05$.

RESULTS

Thymus of the control group appeared atrophied with distorted lobular pattern and loss of demarcation between cortex and medulla. There was widening of the interlobular spaces with increased amount of connective tissue within the capsule and interlobular septa and dilatation of the blood vessels (Fig. 1A). Thymic lobules consisted mainly of densely packed, small darkly stained thymocytes, which overshadowed the sparse epithelial cells (Fig. 2).

Thymus of the castrated rats showed restored lobular pattern and thymic histology. The cortex and medulla became more defined with clear demarcation between them (Fig. 1B). The darkly stained cortex contained more thymocytes with mitotically active lymphoblasts. Pyknotic thymocyte nuclei, which are normally abundant in the cortex, were rarely seen (Figs. 3, 4). The paler medulla consisted mainly of epithelial reticular cells and Hassal's corpuscles (Fig. 4). The epithelial reticular cells were seen among thymocytes both in the cortex and medulla but were more abundant in the medulla. Their nuclei were rounded to oval, pale stained with one or more nucleoli. The cytoplasm of the epithelial reticulum cells was P.A.S. positive and had many cytoplasmic protrusions (Figs. 3, 4).

Mast cells and plasma cells: Mast cells, in all thymuses examined, were selectively located in the capsule and septa but were more abundant in the control group in comparison to the castrated group (Figs. 5A, B). On the other hand, plasma cells in the castrated group were seen in clusters in the cortex, medulla, around blood vessels and in the connective tissue septa (Fig. 5C) while in the control group they were fewer and solitarily distributed in the medulla (Fig. 5D).

Immunohistochemistry: S-100 protein immunoperoxidase stain showed that S-100 immunoreactive cells were distributed mainly in the medulla and at the cortico-medullary border with some scattered elements in the cortex. The cells were dendritic in shape and embraced thymocytes with their branched processes; some of these thymocytes showed pyknotic nuclei. The staining was diffuse both in the nucleus and in the cytoplasm. Based on these morphological features, the immunostained elements were identified as interdigitating cells (Figs. 6, 7).

Morphometry and Image Analysis: The thymus underwent regeneration following castration with significant increase in the absolute and relative thymic weights as compared to the sham control group (Table 1). The cortex and medulla of the thymus were not affected to the same extent; the increase in thickness was significant in the cortex of the castrated group ($P = 0.002$) than in the medulla ($P = 0.81$). Moreover, the area% occupied by interdigitating cells was significantly decreased in the castrated group both in the cortex ($P = 0.02$) and the medulla ($P = 0.03$) (Table 2).

Table 1: Effect of orchidectomy on body and thymus weight.

	Control (mean ± SD)	Castrated (mean ± SD)
Body weight (g)	234.0 ± 2.65	233.6 ± 1.14
Absolute thymus weight (g)	0.22 ± 0.02	0.63 ± 0.02*
Relative thymus weight (g/100g)	0.09 ± 0.01	0.27 ± 0.01*

* $P < 0.05$ compared with sham control rats.

Table 2: Effect of orchidectomy on thickness of cortex and medulla, cortex/medulla ratio and area % occupied by IDC.

	Control (mean ± SD)	Castrated (mean ± SD)	P Value
Cortex Thickness (µm)	32.17 ± 9.89	43.3 ± 14.58	0.002 *
Medulla thickness (µm)	48.17 ± 10.79	49.0 ± 18.86	0.81
Cortex/Medulla ratio	0.71 ± 0.28	0.98 ± 0.48	0.008 *
Area % occupied by IDC in cortex	35.00 ± 4.69	19.43 ± 13.56	0.026*
Area % occupied by IDC in medulla	39.86 ± 5.01	27.14 ± 11.10	0.038*

* $P < 0.05$ compared with architectomized control rats.

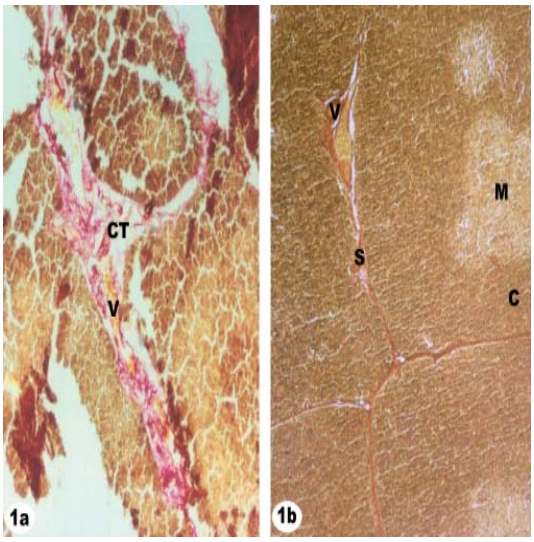

Fig. 1: Photomicrographs of thymus:
A- sham control showing distortion of the lobular pattern of the thymus with loss of thymic tissue and difficulty to distinguish the boundary between cortex and medulla. There is widening of the interlobular spaces with connective tissue (CT) hyperplasia and dilatation of the blood vessels (V).

B- castrated showing an intact lobules with well demarcation between the darkly stained cortex (C) and lightly stained medulla (M). The lobules are partially separated by thin bands of connective tissue septa (S) containing blood vessels (V).
Weigert's haematoxylin and van Gieson's stain; X 40

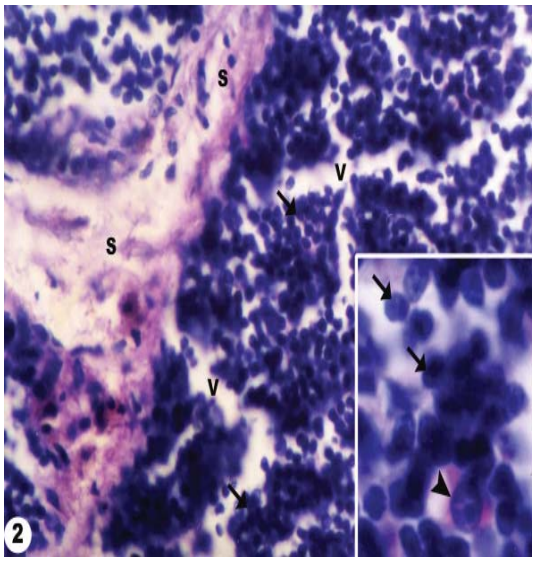

Fig. 2: A photomicrograph of sham control thymus showing wide connective tissue septum (S) with occasional lymphocytes. Abundant small lymphocytes populate the cortex (arrows) clumped in between the dilated blood vessels (V). (PAS stain; X400)
Inset: high magnification of the cortex showing small lymphocytes (arrows) and PAS positive epithelial cell (arrowhead). PAS stain; X1000

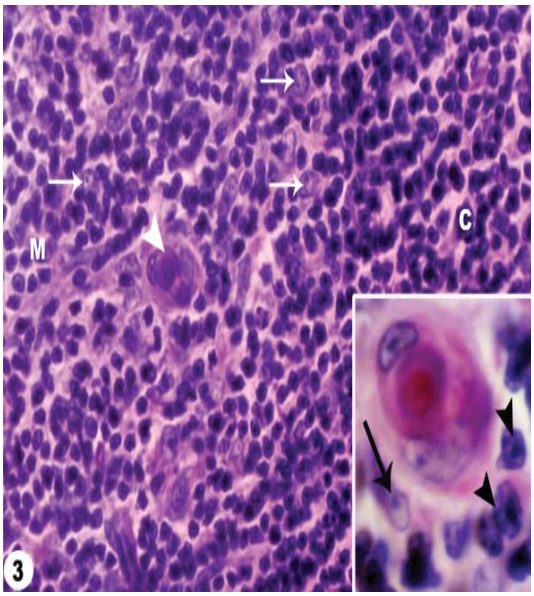

Fig. 3: A photomicrograph of thymus from castrated rat at the cortico/medullary junction showing the cortex (C) and the medulla (M). Abundant small lymphocytes overshadow the sparse epithelial cells (arrows). P.A.S positive Hassal's corpuscle is seen in the medulla (arrowhead).
PAS stain; X400
Inset: high magnification of Hassall's corpuscle showing granular cytoplasm containing a small whorl of keratin appearing material and necrotic debris. The thymic tissue surrounding the Hassall's corpuscles contains epithelial cells (arrow) and mitotic active lymphoblasts (arrowheads).
PAS stain; X1000

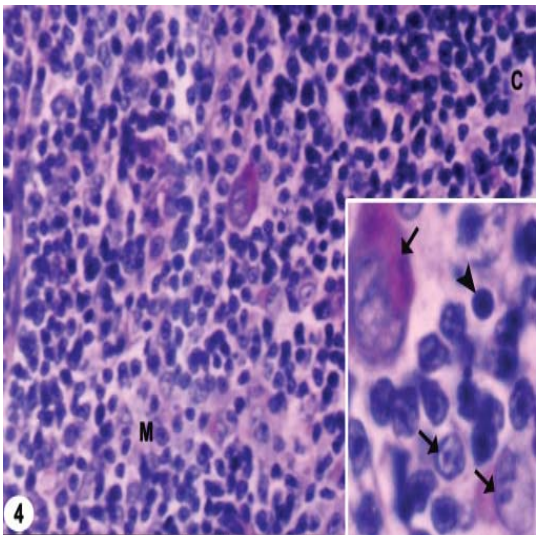

Fig. 4: A photomicrograph of thymus from castrated rat at the cortico/medullary junction showing the cortex (C) and the medulla (M). PAS stain; X400
Inset: high magnification of cortex showing epithelial reticular cells (arrows) with P.A.S. positive cytoplasm, rounded to oval pale stained nuclei with one or more nucleoli. A small pyknotic lymphocyte is seen (arrowhead) among the lymphoblasts.
PAS stain; X1000

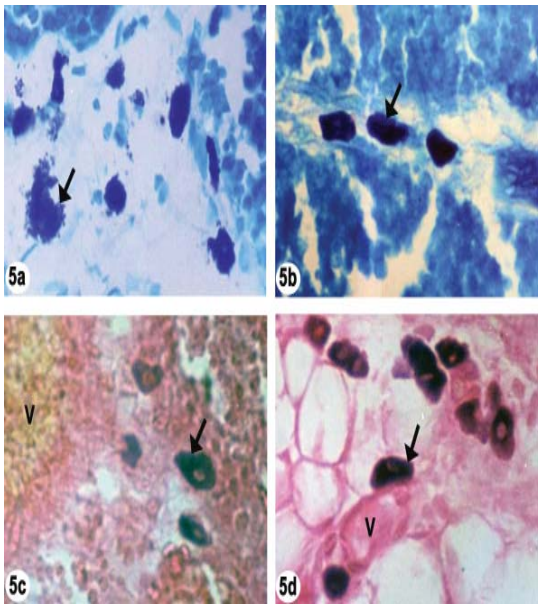

Fig. 5: Thymus sections
A & B- Photomicrographs of thymus from control and castrated rats showing mast cells (arrows) in the capsule and septa.
Unna stain; X400
C & D- Photomicrographs of thymus from control and castrated rats showing plasma cells (arrows) in the cortex and medulla mostly seen close to blood vessel (V).
Methyl green-pyronin; X400

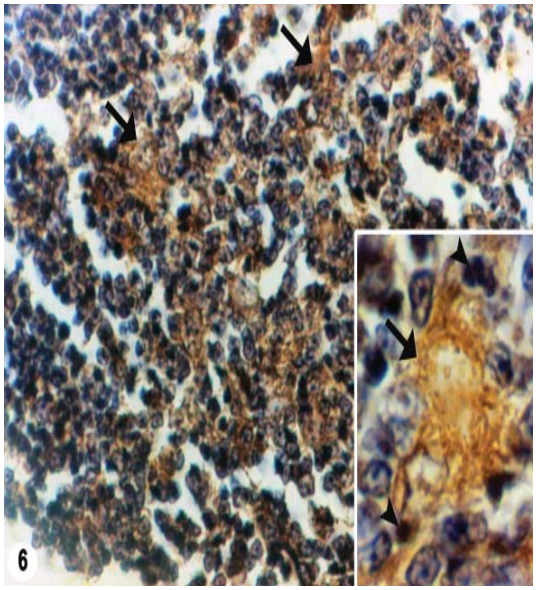

Fig. 6: A photomicrograph of the sham control thymus showing S100 positive cells (arrows).
S100 immunoperoxidase stain; X400
Inset: high magnification showing dendritic cell (arrow) with positively stained S100 cytoplasm and slender processes extending between thymocytes. Some thymocytes have partly destroyed pyknotic nucleus (arrowheads).
S100 immunoperoxidase stain; X1000

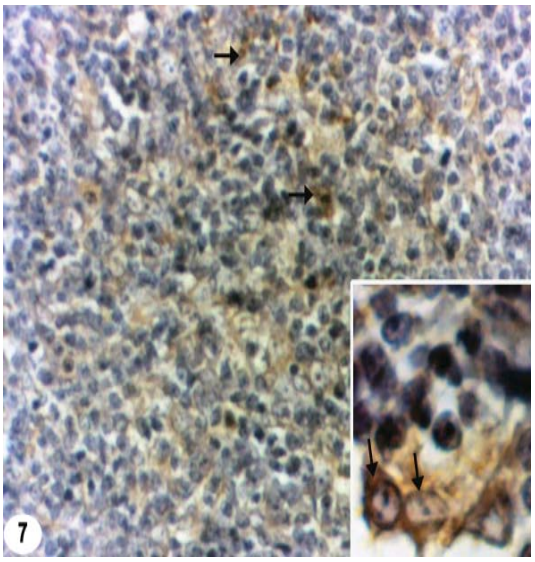

Fig. 7: A photomicrograph of thymus from castrated rats showing abundant lymphocytes with few positively stained dendritic cells (arrows).
S100 immunoperoxidase stain; X400
Inset: high magnification of thymic medulla showing few positive dendritic cells with branching processes and pale stained nucleus (arrows).
S100 immunoperoxidase stain; X1000

DISCUSSION

Testosterone, the principal male sex hormone, is primarily secreted in the testes of males and in small amounts in the ovaries of females and the adrenal glands *(Freeman, et al. 2001)*. The thymus weight and cellularity are influenced by two different groups of factors: one (GH, insulin-like growth factor 1, thyroxine, triiodothyronine, melatonin) causing thymic hypertrophy *(Hirokawa, et al. 1998)* and the other factor is mainly steroid hormones producing thymic atrophy *(Utsuyama & Hirokawa, 1989)*. The balance of their action changes during postnatal life leading to thymic involution. Accordingly, it can be assumed that the changes in thymic structure observed in the present study may be related, directly or indirectly, to changes in testosterone levels after orchidectomy.

In the present study, the thymus of the control rats showed distorted lobular pattern with increased connective tissue content and depletion of the cortical thymocytes. These findings are consistent with age-related changes of the thymus in mammals where thymic involution is associated with a gradual decline in the size and the function of the thymus, which starts at adolescence and progresses with age *(Aspinall and Andrew, 2000;*

Buckland, 2001). The involution of the thymus has been attributed to alteration in the intrathymic T-cell development *(Christianson, et al. 2002)*.

The atrophy of the thymic tissue was more noticeable in the thymic cortex which contains the main bulk of lymphocytes (thymocytes). This could be explained by the fact that cortical thymocytes are especially susceptible to the action of endogenous corticosteroids that lead to either increase in the rate of thymocytes destruction, or a reduction in the rate of bone marrow-derived prothymocyte entry into the thymus, or decrease in the rate of thymocyte production *(Bauer, 2005; Hussar, et al. 2006)*.

In orchidectomized male rats, the large thymic weight gain and the increase in cortex/medullary ratio seen in this study can be attributed to cortical hyperplesia. These findings are in agreement with previous studies which stated that orchidectomy in rats caused involutional effects on the accessory sex organs with trophic effects on the thymus. Moreover, treatment of old male rats with a stable analogue of luteinizing hormone-releasing hormone and the subsequent decrease in testosterone has been shown to result in regeneration of the thymus *(Greenstein, et al. 1987)*. The increase of the size of the thymus may be explained by either increased thymopoiesis as evidenced by the frequent observation of mitotic figures of lymphoblasts or by decrease in their death rate as evidenced by the rare findings of pyknotic nuclei. It is also possible that inhibition of testosterone synthesis and release following orchidectomy not only removes its immunoinhibitory effect on the thymus but also allows other immunoregulatory substances to regenerate the thymus *(Rai & Haldar, 2003)*.

Immunohistochemical analysis and hormone binding assays revealed that androgen effects on the thymus could be exerted through conventional receptor-mediated mechanisms *(Kumar, et al. 1995; Viselli, et al. 1995; Olsen, at al. 2001)* both through the classical intracellular androgen receptor (iAR) and the membrane androgen receptors (mAR) on cell surfaces *(Benten, et al. 2002)*. Cells binding testosterone are localized in the outer thymic cortex (thymocytes) as well as in corticomedullary region and in the medulla (thymic epithelial cells). These results indicate that testosterone has influence upon the function of these cells. Testosterone can modulate T-cell proliferation and/or differentiation, not only directly acting on the T-cell population localized in the outer thymic cortex, but also indirectly by modulating the function of the thymic epithelial cells that bind testosterone and may in turn act secondarily on cortical thymocytes, or their precursors within the thymus *(Leposavic & Micic, 1992; Kumar, et al. 1995; Olsen, et al. 2001)*.

In this study, thymic mast cells were selectively localized in the capsule and septa and exhibited a connective tissue phenotype and were never observed in the thymic parenchyma. The less often observation of mast cells following orchidectomy could be explained by decrease in volume of the connective tissue content of the thymus as a result of its cellular hyperplesia *(Barbini, et al. 1981)*. On the other hand, plasma cells increased following castration and were seen within the parenchyma and around blood vessels. This is in agreement with previous reports which stated that B-lymphopoiesis is negatively regulated by steroid sex hormones and that loss of androgen production or function results in significant increase in B-lymphopoiesis and in the number of peripheral B-cells *(Olsen, et al. 1991; Viselli, et al. 1997)*.

S-100 protein, first detected in the brain, is considered a useful immunohistochemical marker for a subset of dendritic cells, the interdigitating cells, which are mainly located in T-dependent areas of lymphoid tissues *(Ushiki, et al. 1984; Uccini, et al. 1986)*. Thymic interdigitating cells are specialized antigen-presenting cells that play a role in thymocytes negative selection by expression of the major histocompatibility complex (MHC-I and MHC-II). Only thymocytes adapted to self-MHC molecule can survive (2%) and continue to mature the rest will undergo an apoptotic death *(Sprent & Webb, 1995; Ardavin, 1997)*. In the present study immunoreactivity for S-100 protein was demonstrated in large cells with branched processes mainly in the thymic medulla with some scattered elements in the cortex. The decrease in the area% occupied by the interdigitating cells in the castrated rats observed in the present study may be related to the increase of thymocytes which made the interdigitating cells appeared less prominent and not necessarily due to a decrease in the number or size of these cells.

In conclusion, the present findings confirm that thymus is an androgen-responsive tissue. A sig-

nificant increase in thymus weight and cellularity after orchidectomy indicates a significant role for androgens in immune modulation. The exact role of interdigitating cells in age-induced thymic atrophy remain to be elucidated.

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تضخم الغدة التيموسية في الجرذان البيضاء المخصية: دراسة هستوكميائية مناعية

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قسم التشريح ـ كلية الطب – جامعة المنصورة

ملخص البحث

تلعب الغدة التيموسية دور هام فى عمل الجهاز المناعى وتعد من الأعضاء الأوّليّة التى تتأثر بالهرمونات الجنسية، وعليه فإن الهدف من هذا البحث هو دراسة تأثير الإخصاء على التركيب الليمفاوى وغير الليمفاوى للغدة التيموسية وذلك باستخدام الفحص الهستولوجوى والهستولوجى المناعى.

وقد استخدم فى هذا البحث عشرون من ذكور الجرذان البيضاء البالغة. وقسمت الجرذان عشوائيّا إلى مجموعتين (مجموعة ضابطة وأخرى أجرى لها عملية إخصاء). وقد آويت الحيوانات في أقفاص وتلقّوا دخول حر إلى حمية معياريّة وماء للشرب. وبعد أربعة أسابيع من الإخصاء تم التضحّية بالحيوانات عن طريق كسر فقرات العنق. شرّحت الغدة التيموسية ووزنت وتم حساب الوزن المطلق والوزن النسبى (جم/١٠٠جم من وزن الجسم). واستخدم قطاعات من الغدة بسمك (٥ ميكرون) للصباغة بصبغة (ويجرت هيماتوكسلين و فن جسن) لصبغ الأنسجة الليفيّة، و(بيريودك أسيد شيف) للبروتين السكّريّ، و(ميثيل جرين بيرونين) لصبغ الخلايا البلازمية، وصبغة (يونا) لصبغ الخلايا البدنية و صبغة (س-١٠٠) الهستوكيميائية المناعية لصبغ الخلايا المتداخلة.

كان هناك زيادة فى الوزن المطلق والوزن النسبى للغدة التيموسية فى الجرذان التى تعرضت للإخصاء، كما كان هناك زيادة بشكل ملحوظ فى متوسط سمك طبقة القشرة وزيادة فى نسبة متوسط سمك طبقة القشرة الى سمك طبقة اللب وذلك مقارنة بالمجموعة الضابطة. وباستخدام برنامج تحليل الصورة كان هناك نقص فى النسبة المئوية للمساحة التى تشغلها الخلايا المتداخلة فى كل من القشرة واللب للغدة التيموسية للمجموعة التى تعرضت للإخصاء وذلك مقارنة بالمجموعة الضابطة.