The effects of tamoxifen on rat skin

H. S. İnalöz[1], *M.D., M.Sc.*; E. Deveci[2], *Ph.D.*; S. S. İnalöz[2], *Ph.D.*; B. Ünal[2], *M.D., Ph.D.*; A. Eralp[2], *Ph.D.*; I. Can[2]

[1]Department of Dermatology, [2]Department of Histology & Embryology, University of Gaziantep Faculty of Medicine Gaziantep (Turkey)

Summary

Background: Tamoxifen (Tx) is used mostly in the treatment of breast and gynecological cancers. It is also widely used in the treatment of different dermatological disorders. However, its effects on skin have not been investigated previously.

Objective: To investigate the effects of Tx administration on rat skin.

Methods: Forty Spraque-Dawley female newborn rats were separated into two control groups and two experimental groups (n = 10). One day after birth, the control groups of newborn rats were given 0.02 ml saline subcutaneously (sc) daily whereas experimental litters were treated with 100 μg Tx citrate in 0.02 ml saline sc daily for five days. The first control group and experimental group of rats were anesthetized at 21 days whereas the second control group and experimental group of rats were anesthetized on the 28th day. Histopathological assessments were made and compared with the control groups.

Results: Abnormal hair follicles were observed in both experimental groups of rats. Epidermal atrophy together with increased dermal fibrosis was more prominent in the first experimental group. Dermal fibrosis and lymphohistiocytic inflammatory cell infiltration were found to be prominent around the hair follicles in the second experimental group.

Conclusion: Considerable harmful effects of Tx administration were observed on rat skin.

Key words: Tamoxifen; Rat; Skin.

Introduction

Tamoxifen (Tx) is a derivative of the triphenylethlen group of non-steroidal anti-estrogen drugs. It is increasingly used in the treatment of breast and gynecological cancers that affect estrogen-receptors in humans. In dermatological practice, Tx has also been used in the treatment of malignant melanoma [1, 2], autoimmune progesterone dermatitis [3], and desmoid tumor [4]. Some anomalies have been observed in the reproductive systems of rats with Tx administration after birth [5]. However, the effect of Tx on skin has not been investigated previously. Our aim was to investigate the effects of Tx administration on rat skin.

Materials and Methods

Forty Spraque-Dawley female newborn rats were separated into two control groups and two experimental groups (n = 10). One day after birth, the control groups of newborn rats were given 0.02 ml saline subcutaneously (sc) daily whereas experimental litters were treated with 100 μg tamoxifen citrate (Tx) in 0.02 ml saline sc daily for five days. The litters were fed with milk and pellet food during the experiment. The first control and experimental groups of rats were anesthetized at 21 days whereas the second control and experimental groups of rats were anesthetized on the 28th day. Immediately after, biopsies were taken from the perineal skin. Tissue samples were fixed in a solution of 10% formaldehyde. The tissues were then embedded in paraffin wax, serial sectioned and stained with hematoxylin-eosin (H&E) for evaluation using a light microscope. Histopathological assessments were made and compared with the control groups.

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Results

Histopathological examination showed normal epidermis and dermis in the first and second control groups of rats (Figure 1). The most striking changes were observed in the dermis, particularly around the hair follicles in both experimental groups. Epidermal atrophy together with increased dermal fibrosis was more prominent in the first experimental group. Abnormal hair follicles were noticed in this group of rats (Figure 2).

Increased fibrosis and dermal chronic inflammatory cell infiltratration were noticed in the second experimental group of rats (Figure 3). However, the most striking changes were observed around and within the hair follicles. Dermal fibrosis and lymphohistiocytic inflammatory cell infiltration were found to be prominent around the hair follicles in the second experimental group (Figure 4). Overall, strikingly impaired skin maturation was observed with Tx administration in both experimental groups of rats (Table 1).

Table 1. — *Histopathological findings in the experimental groups.*

Histopathological findings	First experimental group (n = 10)	Second experimental group (n = 10)
Abnormal hair follicles	10	10
Atrophic epidermis	10	7
Dermal inflammatory cell infiltratration	7	10
Dermal fibrosis	10	10

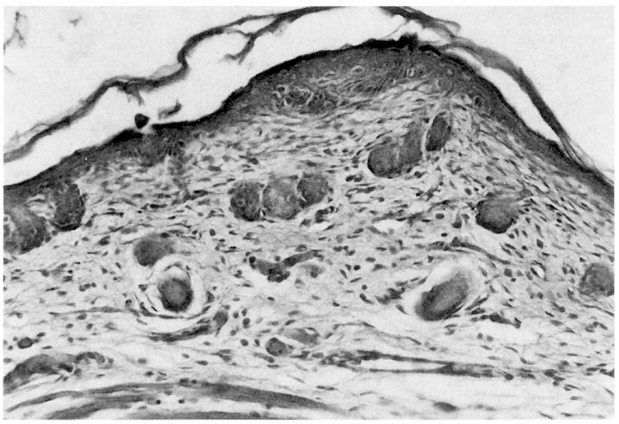

Figure 1. — Normal epidermis and dermis in the first and second control groups of rats (H&E, x100).

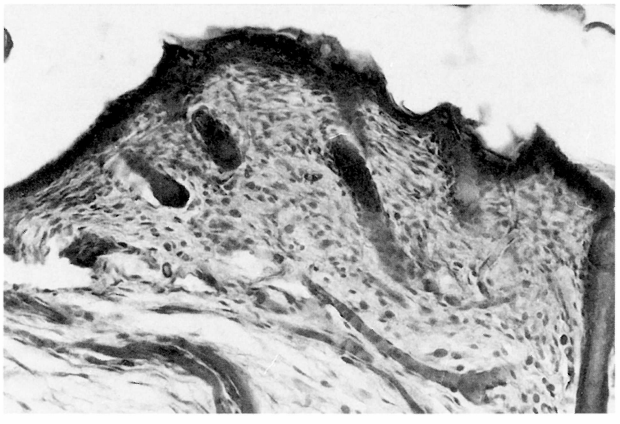

Figure 2. — Abnormal hair follicles and epidermal atrophy together with increased dermal fibrosis in the first experimental group of rats (H&E, x100).

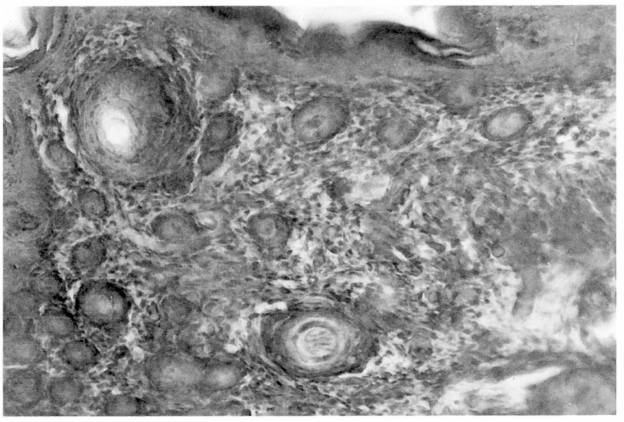

Figure 3. — Increased fibrosis and dermal chronic inflammatory cell infiltration in the second experimental group of rats (H&E, x200).

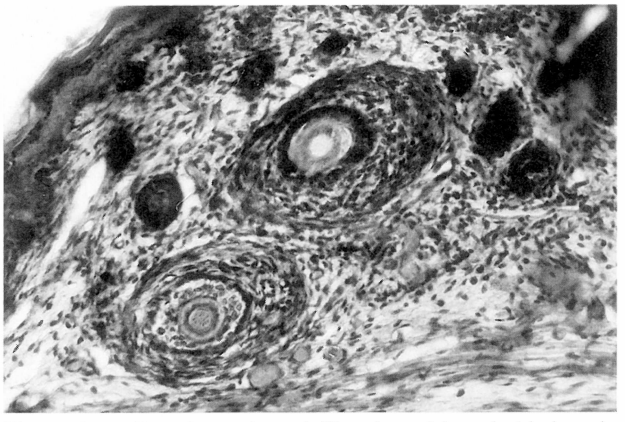

Figure 4. — Prominent dermal fibrosis and lymphohistiocytic inflammatory cell infiltration around the hair follicles in the second experimental group of rats (H&E, x200).

Discussion

The hormone estrogen has effects on many tissues including skin in both males and females. During the last decade, an anti-estrogen drug, Tx, has been increasingly used particularly for primary prevention of breast cancer [6]. Tx has been also used in the treatment of several dermatological disorders. It is the first drug of choice in the treatment of estrogen dermatitis or autoimmune progesterone dermatitis [7]. Tx has been used successfully in combination chemotherapy with carmustine, dacarbazine, and cisplatin in a patient with metastatic melanoma during the second trimester of pregnancy [8]. The anti-carcinogenic and chemopreventive action of Tx was successfully shown by reducing the endogenous and UV light-induced oxidative damage to DNA on skin [9].

Desmoid tumor or musculoaponeurotic fibromatosis is a rare neoplasm of spindle-shaped fibroblasts and collagen which infiltrates muscle and can become adherent to adjacent organs. Pelvic desmoid tumors are common in women of reproductive age and occur particularly after birth. Desmoid cells are known to express estrogen receptors. The proliferation and collagen synthesis of desmoid cells were stimulated by estrogen, and Tx inhibited this effect in experimental studies [3, 10]. In one study, the potential of Tx as an inhibitor of wound contraction has been demonstrated in the treatment of abnormal dermal scarring [11].

The potential risk of long-term use of Tx has not been well established in humans. The main adverse effects of Tx include skin rash and endometrial and myometrial hyperplasia [12, 13]. Venous trombosis and some excess risk of liver, and perhaps gastrointestinal cancers due to prolonged usage have been reported [13, 14]. In an experimental study, in vivo formation of DNA-adducts in mouse skin DNA by Tx administration has been demonstrated [15]. The negative effect of Tx administration has been shown on ossification and chondrogenesis in rats [16].

We observed impaired skin maturation after Tx administration in rats. Anti-estrogens are known to inhibit endothelial cell growth stimulated by angiogenic growth factors and the impaired skin maturation may be related to the antiangiogenic action of the anti-estrogens [17, 18].

References

[1] Dewhurst L. O., Gee J. W., Rennie I. G., MacNeil S.: "Tamoxifen, 17 beta-oestradiol and the calmodulin antagonist J8 inhibit human melanoma cell invasion through fibronectin". *Br. J. Cancer*, 1997, *75*, 860.

[2] Bezwoda W. R.: "The treatment of disseminated malignant melanoma with special reference to the role of interferons, vinca alkaloids and tamoxifen". *Cancer Treat. Rev.*, 1997, *23*, 17.

[3] Moghadam B. K., Hersini S., Barker B. F.: "Autoimmune progesterone dermatitis and stomatitis". *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.*, 1998, *85*, 537.

[4] Tonelli F., Valanzano R., Brandi M. L.: "Pharmacologic treatment of desmoid tumors in familial adenomatous polyposis: results of an in vitro study". *Surgery*, 1994, *115*, 473.

[5] Deveci E., Onen A., Tacar O., Yildirim A.: "The effect of tamoxifen on the neonatal development of rat glans penis". *Clin. Exp. Obstet. Gynecol.*, 1997, *24*, 237.

[6] Gustafsson J. A.: "Therapeutic potential of selective estrogen receptor modulators". *Curr. Opin. Chem. Biol.*, 1998, *2*, 508.

[7] Kumar A., Georgouras K. E.: "Oestrogen dermatitis". *Austral. J. Dermatol.*, 1999, *40*, 96.

[8] Dipaola R. S., Goodin S., Ratzell M., Florczyk M., Karp G., Ravikumar T. S.: "Chemotherapy for metastatic melanoma during pregnancy". *Gynecol. Oncol.*, 1997, *66*, 526.

[9] Wei H., Cai Q., Tian L., Lebwohl M.: "Tamoxifen reduces endogenous and UV light-induced oxidative damage to DNA, lipid and protein in vitro and in vivo". *Carcinogenesis*, 1998, *19*, 1013.

[10] Chao A. S., Lai C. H., Hsueh S., Chen C. S., Yang Y. C., Soong Y. K.: "Successful treatment of recurrent pelvic desmoid tumour with tamoxifen: case report". *Hum. Reprod.*, 2000, *15*, 311.

[11] Hu D., Hughes M. A., Cherry G. W.: "Topical tamoxifen-a potential therapeutic regime in treating excessive dermal scarring?". *Br. J. Plast. Surg.*, 1998, *51*, 462.

[12] Descamps V., Bouscarat F., Boui M., Marck Y., Lebrun-Vignes B., Crickx B., Belaich S.: "Delayed appearance of maculopapular eruptions induced by tamoxifen". *Ann. Dermatol. Venereol.*, 1999, *126*, 716.

[13] La Vecchia C., Tavani A., Garattini S.:"Adverse effects of preventive therapy in humans". *IARC Sci. Publ.*, 1996, *139*, 135.

[14] Weitz I. C., Israel V. K., Liebman H. A.: "Tamoxifen-associated venous thrombosis and activated protein C resistance due to factor V Leiden". *Cancer*, 1997, *79*, 2024.

[15] Cai Q., Wei H.: "In vivo formation of DNA-adducts in mouse skin DNA by tamoxifen". *Cancer Lett.*, 1995, *92*, 187.

[16] Iguchi T., Irisawa S., Uchima F. D. A., Takasugi N.: "Permanent chondrification in the pelvis and occurence of hernias in mice treated neonatally with tamoxifen". *Reprod. Toxicol.*, 1988, *2*, 127.

[17] Xiao X., Hong L., Sheng M.: "Promoting effect of estrogen on the proliferation of hemangioma vascular endothelial cells in vitro". *J. Pediatr. Surg.*, 1999, *34*, 1603.

[18] Gagliardi A. R, Hennig B., Collins D. C.: "Antiestrogens inhibit endothelial cell growth stimulated by angiogenic growth factors". *Anticancer Res.*, 1996, *16*(3A), 1101.

Address reprint requests to:
H. S. İNALÖZ
Department of Dermatology
University of Gaziantep Faculty of Medicine,
Kilis Yolu Üzeri
27310 Gaziantep (Turkey)