

## EXPRESSION OF ESTROGEN AND PROGESTERONE RECEPTORS IN SUBCUTANEOUS ENDOMETRIOSIS

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**Abstract** - Endometriosis is a clinical disorder defined by the presence of functional endometrial tissue outside the uterine cavity. Depending on the localization of the endometrial tissue related to the pelvis, the endometriosis can be classified either as intrinsic or extrinsic. The prevalence of endometriosis is difficult to determine. Statistical data show that endometriosis could be associated both with female infertility (20%) and pelvic pains (24%), while in 4.1% of affected women, endometriosis has asymptomatic forms. The total prevalence of endometriosis is estimated to be between 5-10%. A 35-year-old woman from Knic, Serbia, was admitted to the Obstetrics and Gynecology Clinic of the Clinical Center in Kragujevac for surgical treatment of a suspicious swelling in the pubic region. Following surgical intervention, a nut-sized tumor was removed and sent for both pathohistological and immunohistochemical analysis. The results confirmed the presence of subcutaneous endometriosis positive for both estrogen and progesterone receptors. Endometriosis is usually described as a steroid hormone-dependent change that resembles the eutopic endometrial tissue characteristic for the presence of both glandular and stromal tissues. Given the fact that endometrial lesions are estrogen-dependent tumors, a crucial factor in the development of endometriosis is a late exposure to the hormone, mostly estrogen. Spontaneous subcutaneous endometriosis is rarely observed, but it could be assumed if there is recurrent pelvic pain which intensifies during menstruation. Given the fact that endometriosis coexists with different autoimmune diseases, multidisciplinary approaches are required for its proper diagnosis.

**Keywords:** Estrogen receptor, progesterone receptor, subcutaneous endometriosis,.

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### INTRODUCTION

Endometriosis is one of the most common gynecological benign diseases in which functionally active endometrial cells are deposited in areas outside the uterus. In the literature, endometriosis is classified either as intrinsic or extrinsic, depending on its localization in relation to the pelvis (Attia et al. 2000). Intrapelvic endometriosis presents itself as the existence of endometrial tissue within the uterine cavity, while extrapelvic endometriosis may occur anywhere in a woman's body (Kyama et al. 2007, Badawy et al. 2003).

Endometriosis may not only occur asymptotically in the 4.1% of the women who undergo lapa-

roscopic intervention of ovarian ligatures, but also in the 20% of women with infertility, and the 24% of women with pelvic pain (Chapron et al. 1999). The overall prevalence of endometriosis is estimated to be roughly 5-10%. The chronic pain in the pelvic area that is mainly manifested in dyspareunia, dysuria, menstruation and other diseases, usually follows endometriosis (Attia et al. 2000, Woodward et al. 2001).

One of the oldest theories explaining the origin of endometriosis suggests that the key factor in the development of endometriosis is the reflux of endometrial debris with the menstrual blood flow

through the fallopian tubes into the peritoneal cavity and its retention in both the ovaries and other structures of the small pelvis. It is well known that about 90% of women have retrograde menstruation at least once or many times during their reproductive period. However, it is still unclear why endometriosis develops in some women, but not in the others.

On the other hand, the theory of metaplasia suggests that both ovarian and peritoneal endometriosis occur due to the metaplasia caused by the mesothelial cells of the pelvis. This theory explains the development of endometriosis in the kidneys specifically in the peritoneal invagination, in the germinative epithelium of the ovaries and in the pelvic peritonum.

The immunological theory explains that ectopic endometrial tissue acts as a foreign body; therefore, it activates the immune system including both cellular and humoral immunity. This theory is mainly based on the occurrence of dissemination. The dissemination of endometrial cells can be done either by blood or the lymphatic system into peripheral organs. However, endometriosis rarely develops in either the lymphatic system or the glands. The fault of this theory is its inability to explain the occurrence of endometriosis in the pleural cavity and in the other peripheral organs arising mostly from metaplasia of the endometrial epithelium (Woodward *et al.* 2001, Seleem *et al.* 2002, Olive *et al.* 1993). The differential diagnosis of endometriosis depends on the localization of the active endometrial tissue and the size of the endometrial tumor mass. The dominant symptoms of endometriosis are infertility, pelvic joint pain, dyspareunia, dysuria, and menstrual irregularity (Landi *et al.* 2006, Ostric *et al.* 2006, Wicherek *et al.* 2006).

## MATERIALS AND METHODS

A 35-year-old woman from Knin was admitted to the Obstetrics and Gynecology Clinic of the Clinical Center in Kragujevac on March 3rd 2009 for surgical treatment of endometriosis in the pubic region. The distribution of pubic hair and secondary sexual characteristics were normal. According to the gynecological

history, the menarche occurred at the age of 11 and was followed by irregular cycle lasting 20-22 days, followed by heavy bleeding. She denied having any previous gynecological diseases. She had three full term pregnancies and delivered three children by normal birth; the last delivery occurred eight months prior to her hospitalization. She did not have any complications related to the previous pregnancies. Five months prior to hospital admittance, the patient noticed a swelling that was localized in the pubic region (2 centimeters from the medial line) that was painful at the time of menstruation. She underwent surgery under local anesthesia and, a chestnut-size tumor-like mass was removed and sent for both pathohistological and the immunohistochemical analysis. Macroscopically, the tissue sample had a rough surface with dimensions of 32x18 mm. The excised tumor section was colored yellowish-white with solid consistency.

### *Pathohistological findings*

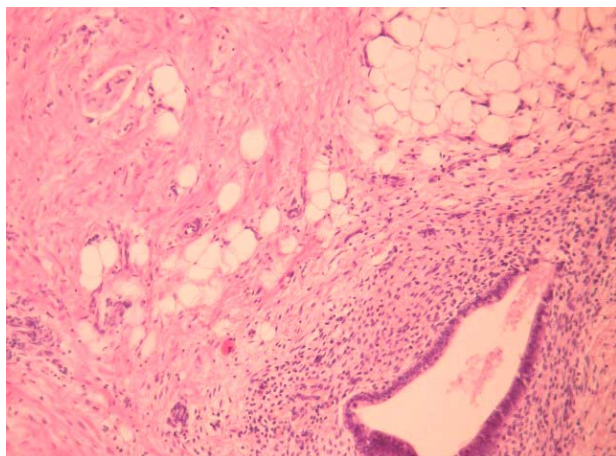
Macroscopically, the tissue sample had the dimensions 35x35x30 mm, a rough surface covered with bare greasy tissue, of a solid consistency, white in color on the section.

Microscopical analysis of the tumor by the hematoxylin and eosin staining method revealed a formation comprised of both fat and connective tissue, with multiple glandular cells varying in shape and the size (Fig. 1). This formation was covered with cylindrical epithelia surrounded by proliferating stromal cells which correspond to the ectopic localization of endometrial mucous membrane. Immunohistochemically, the epithelium and stromal cells of the endometriosis expressed estrogen and progesterone receptors (Figs. 2 and 3).

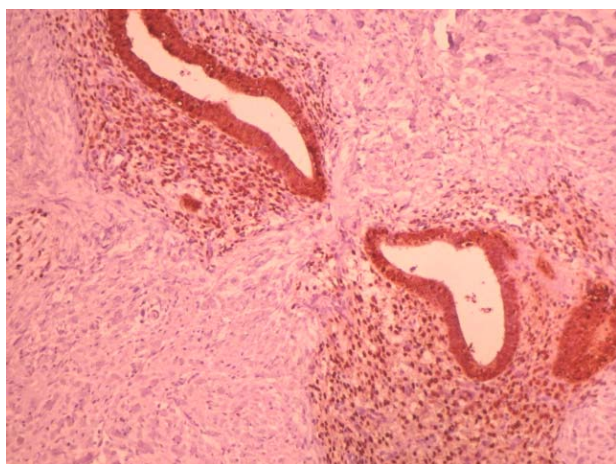
Diagnosis: Endometriosis externa.

## RESULTS AND DISCUSSION

The term endometriosis was first established in 1860 by Rokitansky, who described it as a condition affecting not only humans but the other primates as well (Renner *et al.* 2006, Einspanier *et al.* 2006,



**Fig. 1.** Subcutaneous endometriosis HE 40 X



**Fig. 2.** Subcutaneous endometriosis, Progesterone receptors 100 X

Thapa et al. 2007). Ectopic endometriotic lesions are commonly described as the presence of both endometrial glands and stroma outside the uterus. There are significant biochemical differences between normal (eutopic) and endometriotic tissue. However, there are insufficient data explaining the biochemical differences between the eutopic endometrial tissues of women with endometriosis and those without endometriosis. Previous reports suggested various biochemical differences, including structural anomalies, proliferation, immune component, molecular adhesion and inhibition of proteolytic enzymes. The pathological analysis of the eutopic endometrial tissues of these women may

vary from microscopic focuses to large endometrial cysts (Sharpe-Timms et al. 2001, Renner et al. 2006). Analysis of the expression level of the progesterone receptors in endometriosis is crucial for understanding the molecular basis of the endometriotic tissue's resistance to progesterone. Knowing the expression level of the progesterone receptors may have pathophysiological significance and may anticipate the effect of progesterone on the target tissue. In addition, the sole localization of the progesterone receptors within either the stromal or glandular cells of the endometriotic tissue is also highly important. Moreover, some studies evaluated the total expression of the progesterone receptors during endometriosis in different phases of the menstrual cycle. It was demonstrated that the expression level of the progesterone receptors of the endometriotic tissue was significantly lower compared to that of the eutopic tissue. However, some studies demonstrated no differences in the expression of progesterone receptors between the endometriotic tissue and the endometrial tissue during the proliferative phase of the menstrual cycle. On the other hand, the expression levels of both the estrogen and progesterone receptors significantly decreased during the secretory phase of the menstrual cycle, whereas the progesterone receptors were mainly localized at the basal layer of the endometrium. The presence of estrogen receptors in the endometrial stroma stimulated an increase of the endometrial proliferative potential, thus leading to high implantation potential of the endometrium. According to some authors, endometriosis originates due to the migration of endometrial basal cells outside the uterine cavity (Attia et al. 2000, D'Hooghe et al. 2003, Leyendecker et al. 2002, Nisolle et al. 1997). Thus, the development of endometriosis is induced by unhealthy life style and environmental influence; however, the real cause of endometriosis is still unknown.

In addition, some studies suggested the consumption of caffeine and alcoholic beverages to play an important role in increasing the risk of developing endometriosis; however, other studies demonstrated the protective role of cigarette smo-

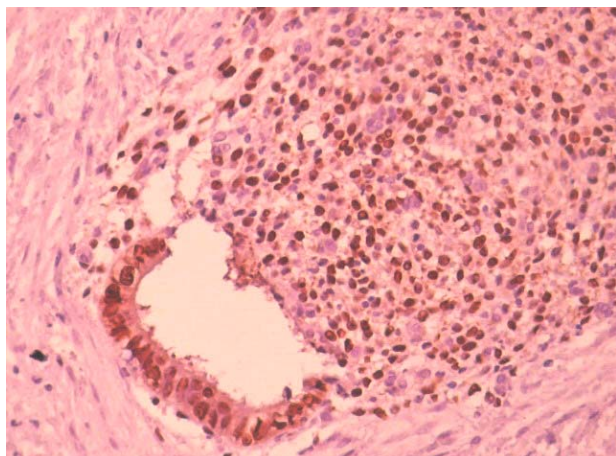


Fig. 3. Subcutaneous endometriosis, Estrogen receptors 200 X

king (Hediger et al. 2005, Freedman et al. 2002). Given the fact that endometrial lesions are estrogen-dependent tumors, the crucial factor in the development of endometriosis is late exposure to estrogen. Moreover, progesterone demonstrates a protective effect on the endometrium during pregnancy. The chronic use of synthetic progesterone results in the inhibition of endometrial growth. The administration of agonists to the gonadotropin releasing hormone (GnRH) causes the atrophy of the endometriotic endothelium through the inhibition of ovarian function and ovulation (Olive et al. 1993, Renner et al. 2006, Sinaii et al. 2002, Giudice et al. 2004). Endometriosis, as a chronic inflammatory pelvic infection, is usually associated with the symptoms of autoimmune diseases including Hashimoto's thyroiditis, systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, the fibromyalgia, allergies, asthma, etc. Patients diagnosed with endometriosis are predisposed to a higher risk of developing ovarian cancer, melanoma and breast carcinoma (Sinaii et al. 2002, Somigliana et al. 2006). Spontaneous subcutaneous endometriosis is quite a rare condition. There are often doubts in diagnosing spontaneous subcutaneous endometriosis. For the proper diagnosis of endometriosis, various significant diagnostic tools must be applied such as ultrasonography, computer tomography and magnetic resonance. In addition, different types of malignant tumors and non-neoplastic disorders must be con-

sidered in the differential diagnosis of endometriosis. Pathohistological verification of the endometriotic tissue sample is required for the proper diagnosis of endometriosis.

To date, endometriosis remains a clinical enigma due to insufficient etiological findings and pathogenesis. Spontaneous subcutaneous endometriosis could be assumed if in the case of recurrent pelvic pain, which intensifies during menstruation. Given the fact that endometriosis coexists with different autoimmune diseases, a multidisciplinary approach is required for its proper diagnosis.

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