Histopathologic Examinations and a Research Field of Endometriosis

Histopatolojik Değerlendirmeler ve Bir Araştırma Alanı Olarak Endometriozis

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ABSTRACT

Endometriosis is an estrogen-dependent diseases associated with pain and infertility with features of most frequently symptoms according chronic inflammation, dysmenorrhoea, deep dyspareunia, dyschezia and dysuria. Functional endometrial and stromal tissue implants exist outside the uterine cavity and causes inflammatory processes. Therefore, several undesirable reactions can occur. There are several diagnostic methods however histopathology is one of the gold standards. This review summarizes the histopathological indications of endometriosis disease with different researches.

Key Words: Endometriosis, endometrium, gland, histopathology, inflammation

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ÖZET

Endometriozis ağrı ve infertilite ile ilişkili östrojen-bağımlı bir hastalık olup en sık görülen semptomlar içerisinde kronik inflamasyon, dismenore, derin disparoni, diskezi ve dizüri yer almaktadır. Fonksiyonel endometrial ve stromal doku implantları rahim boşluğunun dışında bulunur ve inflamatuvar süreçlere neden olur. Bu nedenle, istenmeyen birkaç reaksiyon meydana gelebilir. Birkaç tanı yöntemi vardır ancak histopatoloji altın standartlardan birisidir. Bu derleme, endometriozis hastalığının histopatolojik endikasyonlarını farklı araştırmalarla özetlemektedir.

Anahtar Sözcükler: Bez, endometriozis, endometrium, histopatoloji, inflamasyon

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INTRODUCTION

Endometriosis is a gynecological disease in which functional endometrial and stromal tissue implants exists outside the uterine cavity, leading to inflammatory processes. There is a correlation between abnormal menstrual cycle lengths and endometriosis (1). The contents of the menstrual flow have the ability to adhere and implant on the surface of the ectopic sites by avoiding from apoptosis (2, 3). Within today's knowledge, it is known that uterine cells can abnormally migrate to ectopic sites such as tuba uterine (4), abdominal muscle (5) thorax (6), gastrointestinal tract (7), umbilicus, inguinal area (8) and even sciatic nerve (9). During a normal menstrual cycle, uterus is under an influence of three different processes defined as regeneration, differentiation and shedding under the command of two important ovarian hormones progesterone (P4) and estrogen (E2). The balance of these two hormones are critical for the possible implantation of an embryo however when the uterine cells migrate to ectopic sites, a P4 resistance with an E2 dominance can be seen. As a result, by means of E2 dominance cell proliferation, inflammation and angiogenesis increase; inflammatory cytokines and expression of macrophage exists; pain and infertility can negatively affect woman's life (10, 11). There are different theories based on this disease yet none of them can explain the whole pathogenesis of the endometriosis. The most popular of them is the 'retrograde menstruation hypothesis' which explains that the endometrial fragments can reach and implant onto the peritoneum and, also other abdominal organs starting an inflammation process. Menstrual flow goes backward through the fallopian tubes into the pelvic cavity. Thus, eutopic endometrial cells, growth factors and cytokines have the possibility to proceed through fallopian tubes. As these structures reach the pelvic cavity they are able to penetrate and proliferate on the tissue which is around the cavity; glandular epithelial cells and stromal cells can adhere into peritoneum (12). The retrograde menstruation hypothesis cannot explain the existence of endometriosis in extra pelvic regions such as thoracic cavity or central nervous system. It is known that affected women likely have an immune dysfunction that interferes with the removal of these endometrial debris (13). Endometriosis affects approximately 5% of women of reproductive age (peak at 25-35 years of age), diagnosis is particularly carried out by histological examinations of the lesions and medical therapy or surgery is applied depending on the course of the disease (14).

Theories Related with Endometriosis Disease

Uterus consists of three layers: 1) tunica serosa or as known as perimetrium is a structure of periton which is facing the abdominal cavity, 2) tunica muscularis or known as myometrium is one of the major part of the uterus which is made of smooth muscle fibers, 3) tunica mucosa or known as endometrium the inner layer of uterus contains abundantly blood vessels and glands which menstruation takes part (15, 16). Menstruation cycle (or menstrual bleeding) is defined as small patches of necrotic endometrium separates from the endometrium layer, stratum functionalis, creating menstrual flow (17). During menstrual cycle, endometrium passes three phases following as follicular (or proliferative), secretory and menstrual stage. The proliferative phase begins at the end of the menstrual phase, which is under the influence of estrogen hormone. The corpus luteum secretes progesterone which is a steroid hormone responsible for the decidualization of the endometrium starts the secretory stage 2-3 days after ovulation. When the menstrual phase begins, blood which contains small pieces of stroma and gland escapes from superficial arteries (18). Reformation after corruption of the endometrium functional layer, it is a high probability that endometrium originate from stem cell population due to its regenerative potential (19). There are many types of endometrial stem cells located in peritoneum and pelvic cavity, in menstrual debris or originated from after metaplasia which are named as coelomic epithelial cells and mesenchymal bone marrow stem cells (20). The properties and abilities of these cells can explain how they can develop and exist far away from their locations as in lungs (21), colons (22), peripheral nerves (23) etc. Both estrogen and progesterone hormones can regulate some important stem cell pathways which are included in the pathology of endometriosis diseases. For many reasons (retrograde menstruation etc.), stem cells can migrate to ectopic sites which is a well-established hypothesis and can differ to endometrial glands and stroma where they locate (24). Following an endometrial mesenchymal transition, with a cell invasion into the peritoneum lining, differentiation occurs and finally a growth of endometriotic lesions constitutes all this process (25).

There are different theories for the purpose of explaining the endometriosis mechanism (Table 1). The most validity of them is the retrograde menstruation and the Meyer's coelomic metaplasia theory. Yet, the aetiology of this disease is complex due to its interaction with environmental components, genetic factors, hormones and immune system so none of the theories are able to explain the whole mechanism of the disease.

Table 1 Theories of The Pathogenesis of Endometriosis; According to Ridley (26)

In-situ development	Transplantation
Germinal epithelium of ovary (Waldeyer, 1870)	Implantation
	Retrograde menstruation (Sampson, 1922)
Wolffian cell rests (von Recklinghausen, 1895)	
	Mechanical transplantation (Greenhill, 1942)
Embryonic cell rests (Russell, 1899)	
	Benign Metastasis
Coelomic metaplasia (Meyer, 1919)	Continuous growth (Cullen, 1908)
Metaplasia by hormonal stimulation (Novak, 1931)	Lymphogenous (Halben, 1925; Javert, 1949)
Metaplasia by induction (Levander and Normann, 1955; Merrill, 1966)	Hematogenous (Sampson, 1927)

Meyer's coelomic metaplasia theory suggests that, the cells which exist in the mesothelial lining of the visceral and abdominal peritoneum transforms (metaplasia) into specialized cells constituting the disease. The transformation of the peritoneal cells to endometrium like cells are stimulated by hormones or immunological factors (27). The embryonic cells which were residual from Mullerian duct can be able to develop by the influence of estrogen creating endometriotic lesions; this theory is not sufficient to clarify the lesions located outside the Mullerian duct (28).

Endocrine Mechanisms of Endometriosis

In a normal endometrial layer, both estrogen and progesterone plays role via their receptors to maintain a normal menstrual cycle and a healthy implantation process. When the steroid hormones signaling get disturbed by endometrial tissue located outside the uterine cavity a progesterone resistance and estrogen dominance takes place. This imbalance results in such as inflammation, pelvic pain, abnormal bleeding and most of all infertility (10).

The mechanism of endometriosis development is not yet understood, however it is known as sure that estrogen and estrogen receptors (Eα, Eβ) plays an important role of this estrogen-dependent disease. Estradiol is an active form of estrogen and synthesis at different places; the main organ ovary, particularly in granulosa cells and theca cells; secondly adipose tissue, skin and muscles and finally at endometriotic tissue particularly at endometriotic stromal cells (29). Aromatase P450 is responsible for the conversion of C19 steroids (androgens) to C18 steroids (estrogens) and expresses at different organs, abnormally at endometrium. Aromatase P450 is expressed in both endometriotic tissues and eutopic endometrium.

Furthermore, an enzyme which is to reduce the amount of the high-levels of estradiol to estrone is absent also. With these two descripted cases the high

levels of estradiol which is seen among women with endometriosis can be explicable (30).

Progesterone is a production of corpus luteum and is essential for the continuity of pregnancy. Its receptors are predominantly located in the reproductive organs, mammary glands and central nervous system (31). On a normal luteal phase of a menstrual cycle, progesterone inhibits the functions of endometrial proliferation and regulates the differentiation for the uterine functions. By a deprivation of this hormone signaling in both eutopic and ectopic endometrial tissue, progesterone resistance could lead endometrial cells to be able to survive and proliferate outside the uterine cavity. (32, 33).

Classification of Endometriosis

According to symptoms and fertility status endometriosis is classified as three different types; 1) superficial or peritoneal, 2) ovarian or endometrioma, 3) deep (>5mm in depth) endometriosis.

Peritoneal endometriosis; the first stage of peritoneal endometriosis is the attachment and proliferation of the endometrial tissue on the surface of the peritoneum. Then, with a great support from subperitoneal blood vessels vascularization occurs. Finally, due to peritoneal macrophages an inflammatory process takes part concluding with an intraluminal debris. There are some similarities between eutopic endometrium and peritoneal endometriotic lesions in terms of structural features. Many proliferative glands including columnar or pseudostratified epithelium and stromal vascularization are both similar at eutopic endometrium and peritoneal endometriotic lesions as if they were same tissues. Hence, making a distinction between these tissues are not easy for a histopathologist (34, 35).

Ovarian endometrioma; a continuity can be seen between flat cells of the ovarian surface mesothelium and the epithelium of the endometrioma. It is a hypothesis that metaplasia of ovarian mesothelium under growth factors could lead to intraovarian endometriosis. This view can be supported by the presence of primordial follicles surrounding the endometriotic cysts (34).

Deep endometriosis; rectovaginal septum endometriotic nodules are considering to be the deepest and the most painful endometriosis by a process of metaplasia from Mullerian rests. The nodule develops by the proliferation of smooth muscle which is a result of endometrial gland effect to rectovaginal septum (34).

Transvaginal ultrasonography and magnetic resonance imaging are also used in term of diagnose before any treatment. Diagnose as well as classification is based on diagnostic laparoscopy with a corroboration by a histopathologist (36). Therefore, histopathology is important for a differential diagnosis of this disease.

Pathogenesis of the Diseases

As the refluxed endometrial tissue elimination from the peritoneum is absent, the immune system gets alert with several immunological reactions. Wnt signaling pathways are a group of surface receptor signaling pathways promoting signals from the cell surface into the cytoplasm (24). This signaling includes a cascade regulating development and gives an opportunity for cell perpetuate its lineage, proliferate and regenerate. This signaling pathway is also related with some cancer types including gastrointestinal and breast cancers; melanoma and leukemia (37). Wnt signaling is abnormal activated in cases of endometriosis by virtue of estrogen-progesterone regulation. Estrogen induces the expression of Wnt ligands and progesterone binds to its own receptor and downregulates the Wnt inhibitor related gene leading an elevated expression of Wnt proteins in the environment of the endometrial tissue. As a result, this cascade allows a high transcription of MMP9 (matrix metallopeptidase 9) and VEGF (vascular endothelial growth factor) genes and therefore an opportunity of endometrial cells to migrate. The other estrogen-progesterone hormone related signaling pathways are Hh and Notch signaling. Hh signaling is associated with epithelial mesenchymal transition and Notch is associated with malignant transformation of endometriotic lesions (38).

Ectopic endometrial lesions may trigger pain via neural sprouting of nerve fibers which are located nearly blood vessels. A neurotrophic factor, nerve growth factor (NGF), neuropeptide is in charge of the development, proliferation and survival of neurons is found in elevated levels at peritoneal deep adenomyotic and ovarian endometriosis lesions. In addition, endometriosis related peritoneal fluid contains high levels of tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, IL-8 and cytokines are able to activate nociceptors. NGF can also activate mast cells leading for an inflammation process (39).

Approximately 30-50% of women with endometriosis have fertility problems (40). Disruption of pelvic anatomy due to common endometriosis-related adhesions can cause a mechanical barrier that prevents fertilization. The options of treatments are either expectant management, surgery or assisted reproductive techniques (ART). However, in various study results statistical significance was not achieved or some lower fertilization, implantation and pregnancy rates were encountered (41-43). Disruption of pelvic anatomy due to common endometriosis-related adhesions can cause a mechanical barrier that prevents fertilization. The ectopic endometrial implants can affect embryo implantation via immunity factors. The contents of the peritoneal fluid as mentioned before are harmful for the environment of oocyte or sperm. Lastly, abnormal uterine contractions (PG-related) which occurs at endometriosis may cause embryo implantation failure. It is recommending that, in-vitro fertilization (IVF) should be on the list if; 1) tubal function is compromised 2) male factor is also one of the infertility problems 3) previous treatments have failed (44).

Histopathological Evaluations of the Disease

Menstrual cells have the ability to adhere onto peritoneal surfaces as the menstrual endometrium sheds through the pelvic cavity. These cells can proliferate and survive by avoiding from the immune system. As the lesion growth proceeds, an inflammatory process with locally present cytokines and growth factors occurs in these environments. Also, anti-apoptotic factors increases, pro-apoptotic factors decrease (3). The continuous of the implantation is due to the local production of estrogen. The development of endometrial tissue depends on the formation of the blood vessels. Vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF) -alpha and interleukin (IL) -6 are among the important mediators of angiogenesis. In peritoneal fluids of patients with endometriosis, the concentration of these mediators are responsible for angiogenesis and additionally prostaglandin and macrophage level increase are observed (45, 46). The diagnosis of endometriosis could be combined with clinical examination and imaging findings. Definitive diagnosis is highly possible with histopathological and immunological examinations together. For this purpose, a histological guide of stroma and endometrial gland structures are unique for a verification: 1) cystic cavities surrounded with endometrial epithelium and stroma 2) diffuse hemosiderin-laden macrophages located in stroma 3) cholestrine crystals 4) lymphocytes 5) polymorph leukocytes 6) connective tissue areas 7) vessel sections 8) fresh bleeding areas (47). Eventually, biomarker results of peritoneal fluid, serum, plasma, urinary contents are unique for a best verification.

Models in Endometriosis Research

Different species of animals are widely used to understand and develop new medicines for several diseases. Using laboratory animals for researches are important when there is limitation or non-opportunity for scientists to solve the main problem which is behind the inaccurate structural mechanism. It is substantial to choose the right animal type which will successfully represent the model. Menstrual shedding is a condition for the development of endometriosis and therefor it can normally occur in humans and some non-human primates. The transplantation of the endometrial tissue to the ectopic site is easy for small laboratory animals so scientists prefer rodents as experimental animal models. Transplantation is prepared for rodent models and there are two different types of this endometriosis model; homologous and heterologous model. At this point, application of the homologous model is required when the animal model doesn't have its own system which will cause the effects of a ''normal endometrial tissue (glands and stroma) spreading outside the uterine cavity'' outcome. So the researcher must replace the endometrial tissue by manual intervention to the ''wrong place'' for an ectopic site result. For this, a piece of uterine tissue for example approximately 5mm-1cm is transplanted onto the surface of the anterior abdominal wall facing the peritoneal cavity (Figure 1) (48).

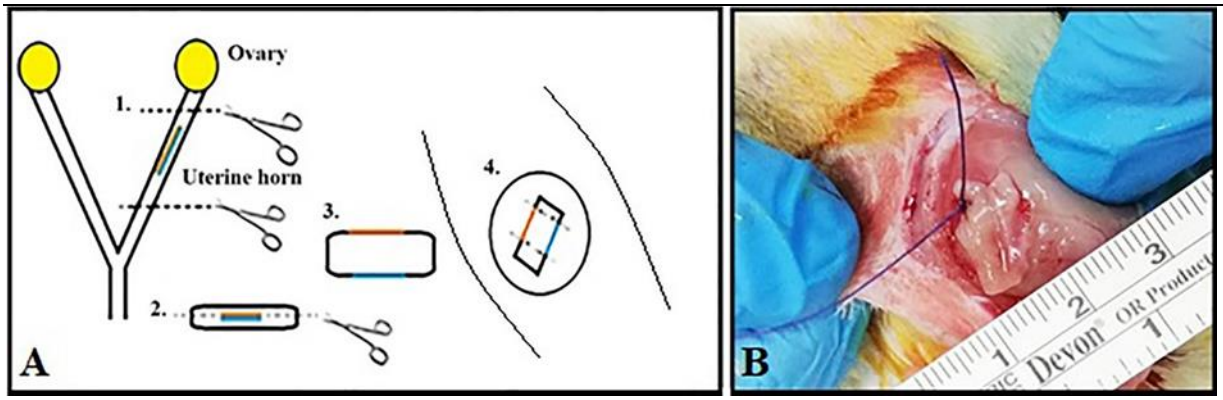

Figure 1 A schema of the procedure removing a part of the uterine tissue. The 2nd step demonstrates the cut of the tube form of the uterine horn to be able to suture it onto the anterior abdominal wall as shown as step 4 (A). A picture of an endometriosis experimental model. The endometrial implant which is being sutured on the abdominal wall can be seen as pinkish red (B; this photo is taken from the authors study)

For both rat and mouse when only the endometrium, not endometrium and myometrium together were transplanted, gave the best developmental results (49). On heterologous model, the endometrial explants are obtained from human and injected intraperitoneally or subcutaneously into rats (50). Both models have pros and cons; the fact is the aim of the study. For example, homologous model is used for studying the effects of immune modulating drugs and anti-inflammatory agents beyond endometriosis, the heterologous model is preferred to study therapeutic testing of pharmacological and hormonal modulations, etc. (48, 49).

Related Studies of the Field

Via image technique technology, detecting small/large or superficial/deep endometriotic implants in human/animal are doable. For example, a research team injected a radiopharmaceutical matter, 18F-fluorocholine ([18F] FCH), by intravenous way to rats in order to image endometrial implants by using positron emission tomography (PET). With a support of these images both of their histological and PET outcomes helped them diagnosing endometrial glandular epithelium and endometrial stroma (51). The most used dye upon histology studies, hematoxylin, is a chemical extracted from a tree named Hematoxylon campechianum which was first discovered by Yucatan in 1502. Hematoxylin stains the basophilic structures as blue, dark blue and black in the cell/tissue. The basophilic organelles in the cells are the nucleus, rough endoplasmic reticulum, and ribosomes. Fibroblasts are also basophilic structures in the tissue. This dye is not only for normal healthy tissues it can also be used for example diagnosing acinic cell carcinoma or malakoplakia because of the presence of the basophilic granules or inclusions locations. Eosin is an acidic dye which is commemorated together with hematoxylin; the pink or orange color contrasts with the blue or black of the hematoxylin. The acidophilic structures are some organelles, the extracellular matrix and the smooth muscle. Not only for healthy tissue eosin can help us to diagnose some values for their eosinophilic globules as for polycystic adenosis of salivary gland or solid pseudopapillary tumor of pancreas (52, 53). By evaluating the microscope images endometriotic tissue contains three predominant cell types; stromal cells, surface epithelium, glandular epithelium (54) and a hemosiderin structure (55). Endometrial glands are lined by pseudocolumnar epithelium and surrounded by large, polygonal shaped decidualized stromal cells. Hemosiderin-laden macrophages scattered around the area joined with a rich neutrophilic inflammation could also be available. Pseudocolumnar epithelium, stromal cells and hemosiderin-laden macrophages can be stained with H&E; for a perfect stromal cell staining, immunohistochemical stain for CD10 is recommended. Stroma is positive for vimentin and CD10 (Neprilisin); additionally, week for estrogen receptors and negative for progesterone (56).

As it mentioned before, there are different types of endometriosis depending on where the lesion is located but the structures are commonly. According to Istrate-Ofiteru et al., with their clinical research using 28 endometriosis cases, on the abdominal wall, peritoneal pelvic and ovarian endometriosis the endometrial glandular tissue can contain simple stratified epithelia. Besides, at abdominal wall endometriosis, a large number of plasma cells, mast cells, macrophages and B lymph cells can be observed around the endometriosis foci (57).

Metzger et al., comprised a standard histologic dating criteria using intrauterine endometrium samples collected from 196 patients between the years 1964 to 1984. They designed four different types of endometriotic implants which were encountered in reviewing these samples: isolated glands with stroma, cluster of glands with stroma, cystic glands and endometriomas. The score scale was from 0 when a gland with non-discernible stroma to 4 where multiple glands encirclement by rims of stroma cells bear semblance to normal endometrium. This histological identification has less cost with fast solution. Also, they identified the extent of fibrosis, presence of surface epithelium and focal hemorrhage within the endometriotic implants (54).

There are many new treatment strategies, the newest one is a research from Oregon State University which focuses on a nanotechnology-based treatment in case of both spotting the place of the endometrial lesions and burning them in their locations thanks to the ability of the particles which can soar to 115 degrees Fahrenheit in mice (58).

CONCLUSION

This review emphasizes some histopathology, pathogenesis and endocrine mechanisms additionally with experimental and some related studies. Endometriosis is a very complex disease with several unknowns. Nevertheless, histopathology is very important in both differential diagnosis and classification of endometriosis. For this, histopathological analyzes can be very useful guides in terms of studying this disease.

Conflict of interest

No conflict of interest was declared by the authors.

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