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Pathogenesis and Morphological Alterations in Endometriosis

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Abstract

Background: Endometriosis is a gynecological pathology found predominantly in reproductive age women suffering from infertility problems. Nevertheless, this chronic condition may develop in postmenopausal females, as well as in men. The complexity of the pathology coupled with the diversity of focal morphological alterations has made the clinical presentation of this disease wide and multifactorial. The histopathological examination may represent a key feature for the diagnosis of endometriosis. However, it is worth to note that many architectural and cytological alterations could make difficult a differential diagnosis of the pathology.

Aims: The purpose of our study was to evaluate histopathological features and morphological alterations in diagnosed patients with pelvic and extrapelvic endometriosis in order to provide an accurate approach for differential diagnosis.

Methods: Our research group performed a 10-year retrospective study, yielding proven cases diagnosed with endometriosis. Data on age, location, clinical diagnosis, prevalence of comorbid diseases, and macro or microscopic changes were recorded and statistically evaluated for a clinical orientation to differential diagnosis.

Results and Conclusions: Our results found that endometriosis is a condition that affects a significant percentage of women in their reproductive age, and is manifested more frequently with pelvic locations compared to extrapelvic ones. The pathological diagnosis does not always correlate with clinical outcomes, due to extensive histopathological alterations that derive from different biological mechanisms of the disease, hormonal alterations (hemorrhage, epithelial glandular hyperplasia, etc.), inflammation and fibrosis, metaplasia and dysplasia.

Keywords: endometriosis, extrapelvic, pathological alterations

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INTRODUCTION

Endometriosis is described as the presence of endometrial glands and stroma outside the uterine cavity. Sampson in the 1940s has defined it as a clinical entity, for the first time (1). Since then, a growing body of evidence has documented the clinical importance of endometriosis and a great interest by gynecologists, histopathologists and surgeons has been shown in order to unravel its physiopathology and to develop the correct treatment protocols. According to literature data, endometriosis is a common gynecological pathology affecting 5-15% of women in their reproductive age and 3-5% of postmenopausal women. It is ranked as one of the most common causes of infertility. Indeed, case reports data have reported that about 15-20% of women with infertility problems and 40-60% of women with dysmenorrhea suffer from endometriosis (2). Furthermore, men undergoing long-term estrogen therapy might be affected (3, 4). In developed countries, endometriosis is considered as one of the most common causes of hospitalization among reproductive-age women (5).

Nowadays, endometriosis is classified as a multifactorial and polygenic disorder (6) that can occur in various tissue sites. Pelvic endometriosis is the most common and accounts for about 96% of all cases diagnosed with ovarian, fallopian or rotundum ligaments endometriosis (2). Despite the rarity of extrapelvic localization (only 4% of all cases diagnosed with endometriosis), other regions has been reported to be affected, thus making their diagnoses more difficult. In this regard, literature data has reported clinical cases of endometriosis in the abdominal wall (2.8% of all diagnosed cases), in the gastrointestinal tract (0.3%), in the urinary tract (0.2%) and in rare sites such as pulmonary, peripheral and central nervous system (0.7%) (7, 8, 9, 10, 11).

The clinical presentation of endometriosis is discrete and depends on the location of the pathology, as well as on the hormonal status of the patient. Being a hormone-related disease, it presents not only a clinical but also histopathological variability resulting in diagnostic difficulties. Analysis misinterpretations are also augmented by the widespread inflammatory reaction promoted by the pathology.

METHODS

Patients diagnosed with endometriosis who underwent surgical procedures, as well as patients with different clinic diagnosis and histological confirmation of endometriosis as primary disease or accompanying one, were included in the present study. This 10-year retrospective study included data collected from the Center of Pathological Anatomy QSUT, the Laboratory of Pathological Anatomy at the Oncology Hospital, the Medical Studio of Prof. Dr. Mehdi Alimehmeti & Prof. Dr. Jera Kruja, the Histopathology Laboratories of Hygeia Hospital, the pathological Laboratory of American Hospital and La Vita Clinic.

Pathological reports were re-evaluated by two histopathologists and all the histopathological lesions were analyzed under microscopic examination. The following patient characteristics

were recorded: age, lesion area and accompanying pathologies. When it was possible and applicable, immunohistochemistry examination was performed by using CD10, ER, PR, p53 antibodies to confirm the uterine origin in the extrapelvic endometrium and its oncogenes tendency.

Collected data were classified according to age, lesion area, histopathological changes, antibody expression, and analyzed for statistical analysis.

RESULTS

We found 72 cases of endometriosis diagnosed either as primary pathology, or as accompanying pathology. The age range was from 21 to 69 years and all patients were women. The overall mean age was 34.1 years and the data were classified as shown in Table 1. The percentage of women with endometriosis at the fertile age (20-44 years old) was about 84.7% (61/72), perimenopause age patients (45-55 years old) comprised about 13.8% (10/72) and only 1.5% (1/72) were postmenopausal women (> 55 years old).

Table 1. Distribution of patients by age

Reproductive status	Age	Number of patients
Fertile age	20-35 years old	44 (61 %)
	35-45 years old	17 (23.7 %)
Perimenopause	45- 55 years old	10 (13.8%)
Postmenopause	>55 years old	1 (1.5 %)

The majority of cases presented a unilocular distribution and accounted for about 91.6% of all diagnosed cases, while 8.4% of cases presented multilocular changes.

Regarding the localization of the lesion site, the pelvic area comprised the majority of cases (48%), abdominal wall and surgical scars 43% of cases, gastrointestinal tract 7% of cases, urinary system 1% of cases and lymph nodule with 1% of cases (Table 2).

Table 2. Distribution of endometriosis by location

Site	Number of cases	Site	Number of cases
Ovary	31	Appendix	3
Fallopian tube	1	GI (rectum, intestine)	2
Uterine ligamentes	3	Urinary system	1
Abdominal wall	30	Limphonodes	1

Concerning the histopathological features of the studied cases, collected data showed that 91% exhibited the classic hystopathological lesions of endometriosis constructed by glandular and/or stromal endometrium, 59% of cases manifested focused hemorrhage, 95% were accompanied by siderophage and hemosiderosis, 79% reported fibrosis and inflammation and 32% of cases with endometroid cysts. In 9% of cases, the situations were more complex because of the presence of myxoid changes, decidualisation, epithelial metaplasia, dysplasia and atypia, and epithelial hyperplasia (Table 3).

Immunohistochemical analysis performed in 5 cases demonstrated positive results for CD 10, ER/PR markers and negative immunostaining for p53.

Table 3. Histopathological elements in the examined cases

Histopathological elements	Number of cases	Histopathological elements	Number of cases
Glands and stroma	66	Hemorrhage	43
Only glands	6	Siderophage	69
Only stroma	0	Inflammation/ Fibrosis	57
Mixoid changes	1	Epithelial Atypia	3
Decidualisation	2	Epithelial Hyperplasia	1
Epithelial Metaplasia	1	Cystic degenerations	23
Dysplasia	3		

DISCUSSION

Our findings highlight the data reported in literature (2), and confirm that endometriosis is a gynecological pathology found predominantly in reproductive age. It is worth to note that the percentage showed in this study could be lower than other reports because our collected data included patients from abdominal, oncological and emergency surgical clinics, and excluded gynecological clinics where patients were clinically diagnosed with endometriosis or endometrioid cyst. This study restriction has slightly altered the variables of endometriosis site localization, increasing the tendency of extrapelvic localization compared to the pelvic sites reported in literature (12).

The ovary is the most common organ affected by endometriosis, with major clinical manifestations of endometrioid cysts or chocolateones in about 70% of cases and surgical scars in 11.43% of cases (13). Other locations include the gastrointestinal tract (4%) (13), the urinary system (2%) (14), lymph nodes and extra-abdominal organs (1%) including pulmonary (15,16) or central nervous systems (15,17,18). In the present study, we examined two cases of very rare sites; an urethelial site present in a 43-year-old woman with hydronephrosis and a lymph node site in a patient manifesting a lymph node. Interestingly, both cases reported histopathological features of the typically endometriosis.

The exact physiologic mechanism involved in the development of the disease is not clear yet. Many studies have described various pathogenic theories, which can be classified into three major groups: Mylarian metaplasia theory, lymphatic or vascular transplantation theory, as well as the combination of these two theories (19). All of them agree on the need to support these theories with other factors that allow uterine tissue to survive outside the uterus cavity while maintaining the normal physiology of aneutopic endometrium and all the consequences associated with the uterine physiologic cycle out of cavity. Immunological and genetic alterations (20), hormonal disorders linked to progesterone receptors dysfunction (21), angiogenesis and vascular support in implantation (22), and

inflammatory alterations (22,23) create conditions for endometrial ectopic tissue to survive in the micro-environment and to further promote physiopathological changes underlying the endometriosis pathology.

Scientific reports have demonstrated an increasing number of cases with surgical scar endometriosis (8). This rise in cases of skin and abdominal muscles (up to 43%) comes not only as a result of the source of analysis but also in support of one of the endometriosis mechanism (5). Yatrogen transplantation during Caesarian-section interventions has augmented, probably due to the increase in the number of births with this method. Although indirect radiology and laboratory methods could be performed to diagnose endometriosis (24), histopathological features represent the gold line standard for early and accurate diagnosis, particularly in multilocular endometriosis, rare site locations and deep pelvic endometriosis.

As reported in our study (Figure 1), the presence of glandular and stromal component accompanied by hemorrhage, hemosiderosis and chronic inflammatory reaction were characteristic features of the histopathological diagnosis of endometriosis in 91% of the analyzed cases.

Only 8-9% of patients reported other histopathological features that need a particular diagnostic analysis. These histopathological alterations might be linked to cellular adaptation, hormonal influence, cellular metaplasia or chronic inflammation (24). Histopathological alterations were associated with hyperplasia and epithelial dysplasia (Figure 2), stromal metaplasia (Figure 3) with diffused decidualisation.

In the present study we have also encountered cases presented in literature as very rare and with clinical and histopathological diagnostic difficulties. In this regard, we examined a multilocular abdominal endometriosis in a fertile woman undergoing urgent surgical intervention as a result of intestinal obstruction, a clinical suspect for diffuse carcinoma infiltration. Histopathological analysis confirmed the presence of diffuse endometrioid glands in the rectum, jejunum, ovary, omentum and urinary bladder and in some areas associated with endometrial stroma without hemorrhage and inflammation. The glands presented hyperplasia and displasia. Immunohistochemical staining in glands and stroma were positive for endometrial tissue and negative for oncogenes. In these conditions, the metastases from endometrial carcinoma or the primary adenocarcinoma on an existing endometriosis was excluded (Figure 4) (25). Another case reported in our study deals with the scar and ovarian endometriosis with diffuse stromal decidualisation in the absence of pregnancy. Microscopic evaluation showed that all stromal endometrium tissue was undergoing a gestational metaplasia with large eosinophilic cells, with well distinct borders, without atypia or dysplasia and small atrophic endometrial glands (Figure 3). These changes are known to manifest during pregnancy stimulation, but are very rare in absence of pregnancy.

Endometriosis of the urinary tract is very rare. Clinic cases reported in literature account for only 2% of total cases of endometriosis and mainly include vesicle urine (26,27). Only in 0.1-0.4% of cases, it affects the ureter (26). In our Clinic of Pathological Anatomy, a case of a 42-year-old woman with hydronephrosis and suspected of ureter metastasis was reported. Detailed histopathological examinations outlined a case of ureteral endometriosis with urinary obstruction and hydronephrosis. Regardless of the confirmed diagnosis, she is still under treatment for continuous obstruction of the ureter.

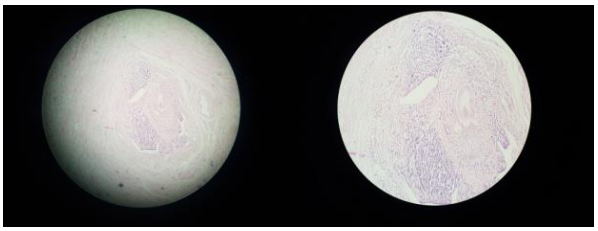


Figure 1. HE stain :endometrial gland and stroma with siderophage and inflammatory infiltrate in muscle fibres.

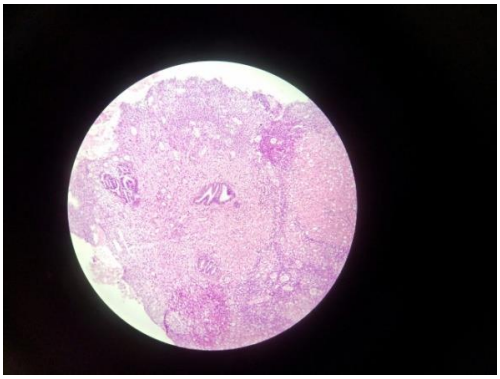


Figure 2. HE stain: epithelial glandular hyperplasia with atypical and dysplasia of endometrial glands. Some of the glands are surrounded by endometrial stroma.

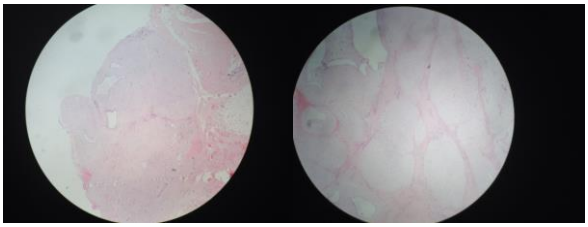
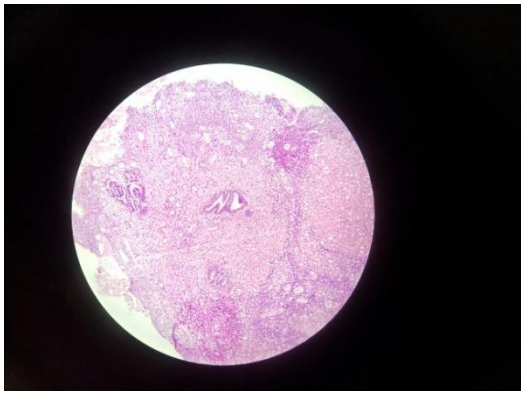
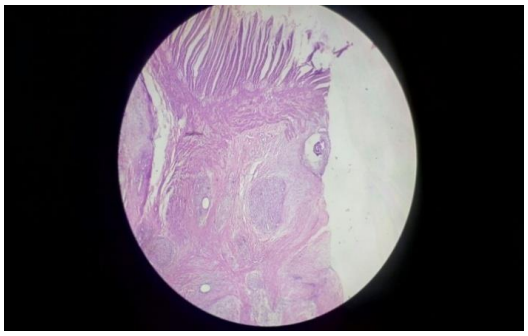


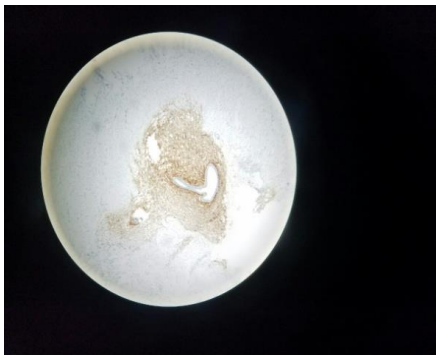
Figure 3. HE stain: microscopic examination of large eosinophilic cells, with well distinct borders, without atypia or dysplasia and small atrophic endometrial glands.

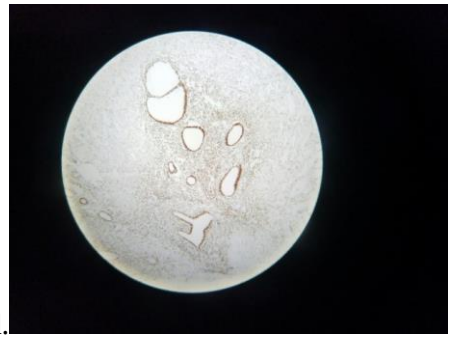
a.



b.



c. 

d. 

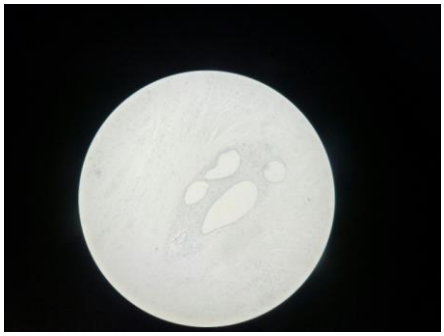
e. 

Figure 4: a. HE stain: epithelial glandular hyperplasia with atypical and dysplasia of endometrial glands; b. HE stain: endometrial glands and stroma in some fields, and in other ones only endometrial stroma; c. CD10 antibody stain by immunohistochemistry reveals the endometrial origin of the stromal tissue; d. ER antibody stain reveal the endometrial glandular origin; e. p53 antibody IHC stain was negative and exclude oncogenic features of the cells.

CONCLUSIONS

Our findings confirmed that endometriosis is a heterogeneous and multifaceted pathology. Although at first glance its histopathologic diagnosis seems to be easily certifiable, a large number of confounding variables should be taken under consideration from both clinicians and histopathologists. A careful and completed examination, along with broad consultations with surgeons, gynecologist and pathologist is mandatory in order to provide accurate diagnosis and appropriate treatments.

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Conflict of interest disclosure: Not available.

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