Review Article

Bowel endometriosis: a benign disease?

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ABSTRACT
Endometriosis is generally assumed to be a benign disease, but it is estimated that 1% of cases is associated with cancer, especially when both conditions are present in the ovary. Extra-ovarian lesions in the rectovaginal septum, colon, bladder, vagina and peritoneum have already been associated with malignancy. Several characteristics of endometrial tissue are similar to the neoplastic phenotype. Endometriosis typically behaves as a neoplastic process by spreading into the adjacent stroma and being associated with distant lesions. This is an update on the diagnostic, clinical and therapeutic knowledge and management of bowel implants of endometrial tissue, as well as on the relation to neoplastic processes, which aims to clarify their benign nature or possible potential for malignancy.

Keywords: Endometriosis. Neoplasms. Intestines.

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Introduction

First described by Rokitansky in 1860,[1] endometriosis is defined as the presence of endometrial gland or stroma outside the uterine cavity.[2] This condition may cause dysmenorrhea, chronic pelvic pain, infertility, dyspareunia and urinary and intestinal disorders during the menstrual flow,[2,3] which thus indicates its hormone-dependent nature.[1]

Even though the available knowledge about endometriosis is still controversial, it is known to affect the peritoneum, ovaries, retrocervical area and bowel,[4,5] and it is one of the major gynecological disorders.[6,7]

Diagnostic suspicion of endometriosis is mainly clinical, based on the aforementioned signs and symptoms caused by the disorder. Studies have been published about possible laboratory tests for the diagnosis of endometriosis,[8] but CA 125 was the only detected marker that can aid in the diagnosis of advanced stages of endometriosis, especially in blood collected within the first three days of the menstrual period.[9] However, invasive methods that allow observing lesions suggestive of the disease and collecting tissue specimens for histological confirmation are still essential for the definitive diagnosis.

In cases that are diagnosed earlier, clinical treatment with hormones is widely used.[10] Surgical treatment is mainly indicated for more advanced cases, based on the clinical picture and imaging exams. Whenever possible, the laparoscopic approach should be used.[7]

Classification of endometriosis

Given the uncertainty over the etiopathogenesis, diagnosis and treatment of endometriosis, as well as its extremely variable behavior, several authors have sought to propose a classification that could render the understanding about this clinical entity universal. Sampson,[11] in 1921, propounded the classification of endometrial hematomas according to the distribution of adhesions, thus indicating the aggressive behavior of the disease and suggesting intestinal involvement.

The American Fertility Society proposed a scoring system for the classification of endometriosis with assignment into stages, similarly to the classification of malignant neoplasias, considering (1) lesion size and the level of involvement (superficial or deep) of the peritoneum or of the right and left ovaries; (2) (partial or total) obliteration of the posterior cul-de-sac; and (3) type of adhesions (velamentous or thick) in ovaries and Fallopian tubes, with total involvement of tubal fimbriae by the adhesions.[12]

With the finding that the depth of invasion of pelvic endometriosis may be significantly larger in women with pelvic

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pain than in those with infertility alone; that such depth was actually larger in older patients; and that the scores established by the American Society of Fertility did not reflect infiltrative lesion, Koninckx and Martin,[13] in 1992, suggested the classification of endometriosis into three types, according to its infiltrative characteristics: (1) type I refers to chronic infiltration into Douglas' cul-de-sac, with larger extension of the disease into the peritoneal surface; (2) type II corresponds to peritoneal disease with intestinal retraction, in the upper portion, preventing the bowel from being accessed; (3) and type III appears in Douglas' cul-de-sac as the tip of an iceberg and is then called *adenomyosis externa*, as endometriosis develops in the smooth muscles of the rectovaginal septum.

Histologically, lesions can be classified into stromal endometriosis (characterized by the presence of stroma that is morphologically similar to the topic endometrium in any phase of the cycle) and glandular endometriosis (characterized by the presence of superficial epithelium or glandular or cystic spaces, associated with tissue with signs of previous hemorrhage). Based on the similarity to the active endometrial epithelium, the glandular pattern is subclassified into (1) well differentiated, when the morphology of epithelial cells does not differ from that of topic endometria in distinct phases of the cycle; (2) undifferentiated, when the epithelium is flattened low, or cuboidal, without a topic endometrial counterpart, resembling the mesothelium of the peritoneal lining or when the epithelium is of the Müllerian type and differs from the endometrial type; and (3) with mixed differentiation, when the previous patterns are present at the same site.[14] The possibility to link histological information with the therapeutic response and prognosis of each case has already been raised.[14-16]

The various aspects of this disorder led Nisolle and Donnez[4] to introduce the concept that endometriosis consists of three different diseases: (1) peritoneal disease, which is characterized by the presence of superficial peritoneal implants; (2) ovarian disease, which comprises superficial ovarian implants and endometriomas, which are the typical cysts of this disorder; (3) and the rectovaginal septum disease.

Bowel endometriosis

The prevalence of bowel endometriosis accounts for 5.3 to 12% of endometriosis cases. Rectum and sigmoid altogether represent 70 to 93% of all intestinal endometrial lesions.[7,17] When the rectum is involved, it may cause obstructive symptoms, making it hard to tell malignant and inflammatory diseases apart.[18]

In a review of 379 cases of extragenital endometriosis, the prevalence was 8.9%, and 32.3% of the cases were found to affect the intestinal wall. The most usual clinical complaint was pain (76.5%), which was cyclic in 41.2% of cases.[19] More specific symptoms, depending on the involvement of the intestinal wall, include rectal pain on defecation extending towards the perineum (52%), constipation or diarrhea (25 to 40%) and alternating symptoms between constipation and diarrhea (14%). About 12% of cases show characteristic symptoms of subacute or acute intestinal obstruction.

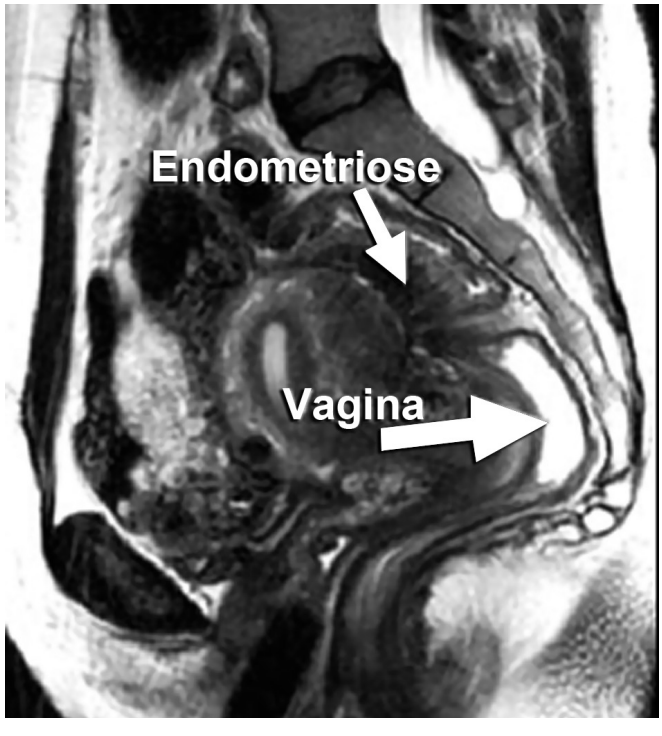
With respect to ancillary imaging exams for the diagnosis of bowel endometriosis, ultrasound scanning (US) has yielded thriving results.[14,20] Transrectal ultrasound is useful in identifying the level of involvement of the intestinal wall.[21] Rectal endoscopic US and colonoscopy have a sensitivity of 100% and specificity of 67%.[14] Rectal echoendoscopy introduced by Ohba et al.[22] has been successfully used as an adjuvant diagnostic method,[7,14] allowing for the identification of the distance between the lesion and the rectal lumen, extrinsic compressions and submucosal rectal lesions. Transvaginal US with intestinal preparation has already shown better sensitivity, specificity, positive and negative predictive values and accuracy than magnetic resonance and digital vaginal examination in cases of rectosigmoid and retrocervical endometriosis, proving to be an important preoperative exam for definition of surgical strategies.[23]

Other adjuvant exams also include fiber-optic colonoscopy (for assessment of extrinsic processes), magnetic resonance (Figure 1) and computed tomography (for assessment of local involvement).[1] Magnetic resonance seems to have better specificity and sensitivity than does CT scan.[24]

However, none of these exams is capable of confirming the diagnosis *per se*. Laparoscopy is still the gold standard, as it determines the degree and extent of the lesions[7,25,26] and allows obtaining tissue specimens and, consequently, the definitive histological diagnosis of the disease. In addition, it is the preferred route of access for surgical treatment, as nowadays there is no room for merely diagnostic laparoscopic procedures.

There exists a paucity of data in the literature on the efficacy of clinical treatment of bowel endometriosis, given that published reports often refer to isolated cases. Some authors recommend

Figura 1 - Magnetic resonance image suggesting deep endometriosis with intestinal involvement



preoperative clinical treatment for reduction of the tissue injury so that surgical intervention can be less aggressive.[27]

Older studies with larger groups of patients report on the results of laparotomy for the surgical treatment of bowel endometriosis.[28] Recently, notwithstanding the smaller sample size, many authors have shown the importance of laparoscopy, especially in elective treatments,[29,30] whose results have been very positive, with no relapses or death, although morbidity rates are still relatively significant.[31] Anyway, the treatment of infiltrative endometriosis is surgical, and the route of access relies on the surgeon's experience and on the location, extension and level of infiltration. The excision of lesions should be made under visualization, sparing the healthy tissue adjacent to the endometriotic nodule and resection should include some portion of the rectal wall and of the posterior cul-de-sac, if necessary. There are cases in which segmental resection of the rectosigmoid may be needed.[7] Figures 2 and 3 show a lesion in the intestinal wall in a surgical specimen.

Figura 2 - Surgical specimen with two endometriotic lesions in the intestinal wall

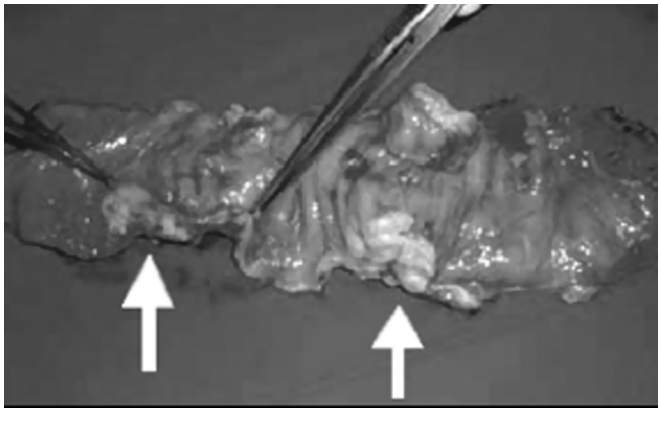
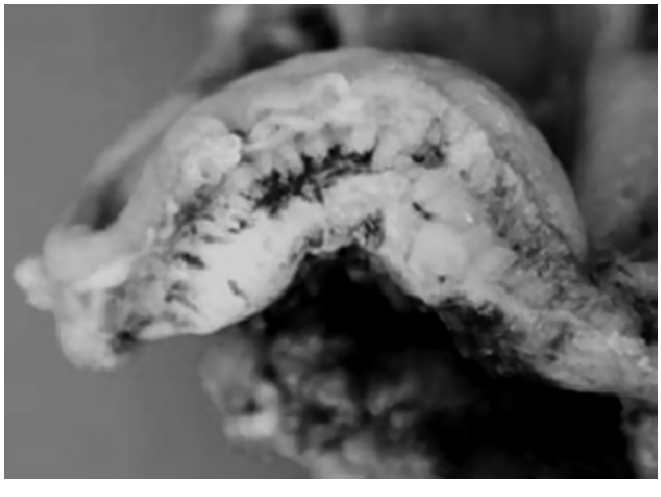


Figura 3 - Detailed view of the surgical specimen with endometriotic lesion with preservation of the mucous layer of the intestinal wal



Usually, the intestinal wall is minimally involved by endometriotic tissue implants no larger than 2 cm. Studies have reported on cases of more advanced lesions that may affect the whole wall, including the intestinal lumen, and cause rectorrhagia, indicating an intestinal endoluminal menstrual process.[44] Another important aspect concerns the association between lesion depth and the circumference of the affected rectum. Abrão et al.[33] observed that lesions with a deeper involvement than the inner muscular layer are related to over 40% of the rectal circumference with microscopic disease.

Changes to the ectopic endometrial tissue are secondary to the physiological menstrual process. A local inflammatory process initially occurs and the subsequent repair phase leads to fibrosis, which in an advanced stage may become irreversible and resistant to hormone therapy. The level and amount of fibrotic tissue found in most women with endometriosis (Figure 3) are closely related to the extent of disease. In the most affected areas, fibrosis can extend into the fat and perivisceral connective tissue.[34]

Kavallaris et al.[35] analyzed specimens of colorectal endometriosis in 7.5-cm segments and found out that the serous layer was involved in the process in 100% of cases; the submucosal and mucosal layers were affected in 34 and 10% of cases, respectively. On the other hand, Anaf et al.[36]noted that lesions were in direct contact with nervous elements in 53% of cases, but they did not find any correlation between the diameter of lesions and the depth of invasion by ectopic implants. Ribeiro et al.[31] assessed 125 patients with bowel endometriosis using rectal US and observed superficial lesions in 9.6% and muscle involvement in 71.2% of cases.

Exeresis of the disc might not be complete in up to 40% of women with bowel endometriosis, in which residual lesion may be present. This incomplete resection apparently results from the fact that the fibrosis of the muscular layer does not always involve intestinal endometriotic lesions.[37]

Endometriosis and Cancer

Although neoplastic processes are less frequent in cases of endometriosis, which has behaved as a benign disease despite constant evolution, 1% of the cases is estimated to be associated with cancer.[38,39]

Indeed, endometriosis has some typically neoplastic characteristics, such as the capacity of invasion into the adjacent stroma and the association with distant lesions.[40] Like cancer, endometriosis can adhere to other tissues, invade them or deform them,[41] even though it does not usually produce consumptive metabolic states.[42] Moreover, etiopathogenic theories on endometriosis include growth factors and cytokines associated with the regulation of cell multiplication and neoangiogenesis, which may play a role in carcinogenesis.[32] Podgaec et al.[44] demonstrated that endometriosis as an inflammatory disease presents some changes in the Th2 component, with a relative increase in the cytokines that represent this pattern of immune response. Also, vascular endothelial growth factors seem to have cyclical variations in the peritoneal fluid in patients with endometriosis,[45] and vascular density and the distribution of the vascular endothelial growth factor and its receptor

are significantly higher in patients with deep endometriosis involving the rectum.[46]

Types of ovarian cancer are usually associated with this condition. Approximately 78% of cases of neoplasias related to endometriosis affect the ovaries, whereas the remaining 22% are associated with extra-ovarian tumors, often found in the rectovaginal septum, colon, bladder, vagina and peritoneum in the pelvic region.[40]

Cellular changes in gynecologic breast tumors have been extensively investigated. Malignant transformation seems to result from changes in the expression of proto-oncogenes and tumor suppressor genes which also play a role in the cell cycle. These changes possibly represent events with an important role in tumorigenesis and in tumor progression, at least in cases of breast tumors.[47]

PTEN gene mutations have already been identified in 21% of endometrioid ovarian cysts.[48] Histochemical studies have also shown that bcl-2 and p53 mutations may be associated with malignant transformation of endometriotic cysts.[49]

According to the concentration of genomic DNA content, cells can be classified into diploid and aneuploid. In general, tumors classified as diploid are associated with a favorable prognosis. This parameter of DNA content does not make a distinction between neoplastic and non-neoplastic lesions, because there are carcinomas and other neoplasias with a diploid pattern.[50] In endometrial tissue obtained from ovarian cysts, a diploid pattern was identified in tissues without morphological atypia and an aneuploid pattern, in atypical tissues.[51] *In vitro* studies have suggested a monoclonal etiology for endometriosis;[52] other authors have observed loss of heterozygosity in 28% of lesions in endometriotic deposits.[53]

Bowel endometriosis and cancer

Several cases of bowel endometriosis have a delayed diagnosis, based on the initial complaint of enterorrhagia and then suspicion of malignant tumorigenesis,[21,54] given that there are no specific pathognomic symptoms of bowel endometriosis, turning the diagnosis into a big challenge.

Li et al[55] reported a case of acute colon obstruction caused by rectal endometriosis, diagnosed only after repeated colonoscopic biopsies and imaging exams which, often could not distinguish the endometriotic lesion from the neoplastic process, leading the authors to recommend further investigation into the risk of malignancy in cases of bowel endometriosis.

Up to 2002, the literature had nine reports of malignant transformation of bowel endometriosis[56-57] and isolated cases have been described in the past 5 years.[58-59] Usually, they are cases of endometrioid carcinomas and rarely do they mean sarcomatous transformation.

The possibility of malignant transformation of bowel endometriosis requires that histological analyses of foci of endometriosis be carried out, especially if we consider that several morphofunctional characteristics of the ectopic endometrial tissue draw it closer to the neoplastic phenotype.[60]

Neoplastic processes associated with bowel endometriosis have proved to be estrogen-dependent, and there was a case report of malignant transformation after progesterone therapy. Kawate et al.[61] reported a case of endometrial adenocarcinoma arising from endometriosis of the mesenterium of the sigmoid colon in a patient submitted to total hysterectomy due to uterine leiomyoma and to hormone replacement therapy. Tumor cells were positive for cytokeratin 7 but negative for cytokeratin 20. The authors ascribed the cause of malignant transformation of endometriosis to hyperestrogenism, especially because the patient had been submitted to hormone replacement therapy for 14 years. They recommended special attention to the outcome of bowel endometriosis in women with history of hormone replacement therapy.

Rojas-Cartagena et al.[62] assessed the role of tumor necrosis factor (TNF) and the involvement of TNF receptors in an experimental model in which bowel endometriosis was surgically induced in female rats. Tissue and fluid samples were analyzed 60 after surgery. The increased expression of TNF and target genes and the low expression of TNF receptor genes revealed involvement of the TNF system in the pathogenesis of bowel endometriosis. Among several mechanisms of action of TNF, one should highlight the mediation of inflammatory manifestations and the destruction of neoplastic cells. The factors associated with TNF receptors have been correlated with the activation of antiapoptotic processes.

Albeit rarely reported, the presence of endometriosis in lymph nodes led some authors to admit the retrograde lymphatic spread of endometriosis.[63] Abrão et al[41] evaluated lesion size, the number of bowel lesions, intestinal wall layers and the circumference of the intestinal loop affected by the endometriotic lesion and the presence of lymph nodes with foci of endometriosis in 35 consecutive cases of bowel endometriosis. The analysis of surgical specimens revealed lymph nodes in the pericolic adipose tissue in 54% of cases and in 26.3% of them, lymph nodes were already compromised by endometriosis. All specimens with endometriotic lesion as thick as or thicker than 1.75 cm showed lymph node involvement, with positive nodes in all cases in which over 80% of the circumference of the intestinal loop was affected by endometriosis. According to the authors, these findings indicate that the assumption that endometriosis is exclusively benign should be reconsidered.

All of these studies undeniably highlight the aggressive behavior of the disease involving the bowel, its differential diagnosis with cancer and the increased probability of concomitant malignant diseases in these patients. The literature does not provide data on DNA ploidy patterns in endometriosis that are specific to the infiltrative lesion in the intestinal wall.[64] Likewise, there is a lack of studies on the balance between cell proliferation and apoptosis in terms of p53 expression in endometrial tissue implant within the intestinal wall. Studies that focus on these cellular aspects will certainly aid in confirming the benign nature of bowel endometriosis, which has been recently questioned by a few authors.

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