Extra-genital endometriosis



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BACKGROUND: Even if endometriosis is usually an exclusively gynecological issue, atypical locations fall within the interest of general surgery. The aim of our retrospective study focuses on the need for surgeons to face this rare condition, in order to avoid unnecessary or inadequate treatment. METHODS: We retrospectively analyzed clinical presentations, previous endometrics diagnosis and surgical acts on a group

of 60 patients, whose mean age was 38.2 years old, with extra-genital endometriosis.

RESULTS: Among the 60 cases of extra-genital endometriosis collected, bowel foci, 37 cases - 61,7% - were the most frequent; then we collected 13 (21.7%) skin, 7 (11.7%) urinary tract and 3 (5%) whole pelvis localizations. It's important to underline the finding of 2 aggressive malignant transformations.

CONCLUSIONS: Extra-genital endometriosis should be considered as a cause of otherwise inexplicable abdominal pain in voung women. Since imaging techniques lack in specificity, we propose explorative laparoscopy as a powerful diagnostic means. Moreover laparoscopy can be turned into a therapeutic act, also limiting the adherences issue, which is associated with this illness and would worsen with open surgery. Extra-genital endometriosis should be treated also to avoid rare, but possible, risk of cancerization.

KEY WORDS: Endometriosis, Extra-genital endometriosis, Laparoscopy

Introduction

Endometriosis is an important finding in the gynecological field. The pathogenesis has not yet been entirely clarified, but the many variable macro and microscopic aspects, the complex problems of therapy it poses, the correlated immune-pathologic aspects, have made it one of the most closely studied diseases in this specialty. In the 1980s, the use of diagnostic laparoscopy spread rapidly in gynecology. It is now done routinely in cases of female infertility and for chronic abdominal pain, and has demonstrated a higher incidence of endometriosis than was previously estimated, as well as an evident relation to sterility. In addition, it has opened new vistas on a disease that cannot be considered truly "gynecological" because it often involves other abdominal (exceptionally also extra-abdominal) organs and the skin, sometimes but not always on a gynecological scar, and can even present in absence of 'gynecological" localizations in patients with no history of the disease.

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Methods

We retrospectively analyzed 60 consecutive cases of extragonadal endometriosis, which were diagnosed at the Pathology Department of our University.

We collected patients data, histological specimens and reports from the Pathology Department. Then we acquired the medical records from departments where these patients were treated, from which we collected anamnesis and surgical reports.

Results

The mean age at the time of diagnosis was 38.2 years old. In 20% of the cases there was either a history of endometriosis or the patient had previously undergone a gynecological operation or caesarean section. In 25% of the cases, a concurrent involvement of at least one genital structure was found during an operation. Finally, in 55% of the cases, whether patients were symptomatic or not, the onset of the disease seemed to be ex novo, and there were no clinical or macroscopic intraoperative data suggesting a secondary localization.

Primitive and secondary rectosigmoidal localizations were the most frequent after the gonadal localization. Of the 60 cases, in 47 patients (78.3%) there was involvement of pelvic organs of the digestive and/or urinary tract, the localization was rectosigmoidal colon in 22 patients (36.7%), appendicular in 10 (16.7%), ileal in 4 (6.7%), bladder in 5 (8.3%), ureteral in 2 (3.3%) and of a hernial sac in 1 patient (1.7%). In the last 3 patients (5%) the whole pelvis was involved, namely the genito-urinary and digestive tracts.

There were 13 skin localizations (1.7%). One was at the level of the umbilicus and symptomatic, since the patient had catamenial bleeding. The most prevalent localization was the supra-public scar in patients who had a cesarean section. In all these patients palpation revealed a subcutaneous hard mass, and was sometimes painful. For all the skin localizations the definitive diagnosis was obtained during histology of the operative specimen (Table I).

TABLE I

Localization	Bowel Sigma-rectum 22(36,7%)	Skin	Urinary tract Bladder 5 (8.3%)	Pelvis
	Appendix 10 (16.7%)		Ureter 2 (3.3%)	
	Ileum 4(6.7%)			
Total: 60	Hernial sac 1(1.7%) 37(61.7%)	13(21.7%)	7(11.6%)	3(5%)

Of the 22 rectosigmoidal localizations, the discovery of endometriosis was made by chance in 3 patients, while in another 7 there was concomitant involvement of one or more genital organs. In 12 cases (54.5%) sigmoid endometriosis was diagnosed in patients who showed no intra-operatively evident genital involvement. These patients reported repeated sub-occlusive episodes (in one case also non catamenial proctorrhagia). Preoperative diagnostic investigations, namely endoscopy with biopsy, CT and MRI scans, did not provide a definitive diagnosis. Rather, in some cases they tended to be misleading, suggesting sub-mucosal cancer due to intact mucosa. A frozen section was always diagnostic but was seldom performed. Some patients who did not undergo this procedure were subjected to highly demolitive surgery for a suspected tumor.

Thus, in most of the patients the diagnosis of endometriosis was obtained only during histology.

A young woman in the 35th week of pregnancy received an emergency operation for bowel perforation due to diverticulitis that was highly singular. The definitive diagnosis was full thickness bowel endometriosis with massive decidual transformation.

Endometriosic foci on the appendix were found in 10 patients. All these were chance findings in an apparently intact appendix removed during surgery for another disease. In 4 of these patients the same foci were found at the genital organs, while 1 had already undergone surgery for endometriosis.

The 4 cases with an ileal localization were stenosing forms. Five patients presented a bladder localization. In 2 cases, during cystoscopy a nodular area was removed and revealed endometriosic foci.

The other 2 cases required a laparotomy and an endometriosic focus was found on the bladder wall.

Two patients with ureteral endometriosis had resection for a stenotic ureter, and in a patient undergoing hernioplasty, endometriosis of the hernial sac was found by chance during histology.

Finally, there were 3 patients with entire pelvis involvement, whose gynecological symptoms were typically associated with hydroureteronephrosis. The most demolitive procedure, not supported by frozen section, was performed in a patient who underwent right hemicolectomy, ovariectomy and ipsilateral nephroureterectomy for a malfunctioning kidney. Histologic examination showed endometriosic foci on the right colon, ileum, some lymph nodes and the ovary.

Another of these patients underwent ureteral resection with T-T anastomosis, resection of the sigmoid and an ovariectomy. Endometriosic foci were found on the colon and ureter. The last patient underwent a laparotomy and biopsy of the rectum wall that was positive for endometriosis, supported by a CT scan that showed a pelvic mass enveloping the ileal loops and colon rectum. In 2 cases, endometrioid carcinoma developed on sigmoid and bladder endometriosic foci, respectively. A 76-year-old patient, who had undergone complete hysterectomy for adenocarcinoma of the endometrium, received an emergency operation for a suspected tumor of the rectosigmoidal junction. Histology, as well as immunohistochemical investigations (CK7+, CK20-, CEA-) suggested an endometriosic origin of the tumor. Two years later the patient underwent a cystectomy and ileal resection for a pelvic adenocarcinoma recurrence, of poorly differentiated clear cell type.

In another case, a 39-year-old patient who had undergone surgery for bilateral endometriosic ovarian cysts, underwent diagnostic laparoscopy for a suspected recurrence and simultaneous resection of an area of the bladder wall that had a hard and thickened, marbled appearance. The final histological diagnosis and immunohistochemical examinations revealed a clear cell adenocarcinoma, which likely originating from an endometriosic focus. Despite radical surgery and subsequent chemotherapy cycles, a few months later the patient had a pelvic tumor recurrence.

Discussion

The definition of endometriosis was first made by Sampson ¹ in 1921. It is a peculiar disorder of the female sex characterized by the presence of endometrial tissue in anomalous sites. It displays a particular predilection for the peritoneum, pelvis and endopelvic viscera ^{2,3} and affects women of fertile age ^{3,4}. Many affected patients have undergone cesarean section or have a positive history for gynecological disease requiring surgery of the genital apparatus ⁵. This chronological succession is almost always present in extra-gonadal localizations involving the abdominal wall, umbilical cicatrix or surgical scars.

The origin of endometriosis is still unknown, although the most accredited metastatic theory postulates that there is a transmigration of endometrial tissue into an ectopic site, initially during "retrograde menstruation". Regardless, the presence of epithelial cells in an ectopic site cannot alone trigger endometriosis development, unless other genetic, hormonal and above all immunologic factors are present ³.

In particular, the immunologic defense mechanisms that should destroy any endometrial tissue, which migrate to the abdominal cavity, seem to be less efficient in women affected by endometriosis. An essential role in the histopathogenesis of endometriosis is played by the inflammatory response to the presence of ectopic endometrium. The histological diagnosis on biopsy or surgical samples is based on the pathognomonic finding of endometrial mucosa foci 6 .

Endometriosic foci, and especially the glandular epithelial component, undergo the same metaplastic (endocervicosis, endosalpingiosis), hyperplastic and dysplastic changes as the endometrium in the anatomical site. Thus, every endometriosis focus must always be very closely examined at optical microscopy to check for any hyperplastic or atypical aspects that could be a prelude to the development of a carcinoma ⁷.

Pelvic pain is one of the most common gynecological symptoms ⁸ and, whether associated with an infertility problem or not, poses a precise indication for diagnostic laparoscopy ⁹.

However, since the advent of the routine use of laparoscopy and the advances in this technique, it is a fact that a progressive increase in the incidence of endometriosis has been observed. Although it is classically a gynecological complaint, it can primarily involve, or co-involve any of the pelvic organs, gonadal or not, all the organs in the abdominal cavity, the extra-abdominal organs and the skin.

Markham et al. ¹⁰ proposed a classification system that subdivides extra-gonadal endometriosis into four classes according to whether the involvement is intestinal, urinary, or extra-pelvic, pleuro-pulmonary or otherwise affecting the skin or nervous system.

Bowel localizations are the most frequent ³, and cause specific symptoms ¹¹ usually associated with more common diseases. The predilection for the sigma-rectum, or bowel portion anatomically nearest to the anterior face of the posterior fornix and uterine isthmus, further supports the migration theory ¹². In the same way, the lesser incidence of an ileal localization (7%) ¹²⁻¹⁵ can be attributed to the peristaltic activity, which by causing continual surface friction, prevents the endometrial cells from taking up residence. In fact, the only ileal tract at risk is the last loop, ¹⁶ which is fixed in proximity to the cecum. The appendix can be affected due to its vicinity to the right tubal ampulla.

Endometriosic lesions sometimes appear as small, multiple nodular formations, mostly situated along the antimesenteric line and, when circumferentially confluent, tend to cause extensive retraction of the bowel wall and stenosis of the lumen ¹².

The process almost never involves the mucosa, ^{12,13,15,16} even when the nodules spread to the submucosa and occupy most of the lumen. In this case digestive hemorrhage during the menstrual cycle is pathognomonic ^{12,15}.

When endometriosis involves the gastrointestinal tract, the clinical presentation ranges from a chance finding to complications ¹⁶. The symptoms are pelvic pain that is only initially catamenial, bowel function complaints ¹³ that pose important problems of differential diagnosis from more frequent diseases, such as tumors, irritable bowel disease, Crohn syndrome, ^{11,14,16} complicated diverticulitis, mesenchymal tumors, other chronic inflammatory disease, ¹² especially if the bowel endometriosis appears as a complication, occlusion ^{13,17-20} or perforation ^{11,21}.

In 80% of the cases, bowel localizations are associated with gynecological endometriosis, ¹¹ so the patient refers dyspareunia, infertility or dysmenorrhea. Although these

symptoms call attention to the genital area, they can also delay the diagnosis of any extra-gynecological localizations.

Radiology can help in cases of suspected intraparietal stenosing or substenosing lesions, whether affecting the whole circumference or not. However, it has poor specificity ^{3,12,15} unless the patient has a clinical history suggesting endometriosis ^{22,23}.

Endoscopy serves to exclude cancer ¹⁶ but is not definitive, largely because of the prevalent sub-mucosal localization. Therefore, even a biopsy is often not diagnostic ^{12,15}. Some success has be achieved with biopsies performed in patients with intermittent hematochezia and with US-guided biopsies ¹⁵ during US-endoscopy, which is undoubtedly preferable because it reveals the degree of wall involvement of the lesion.

The urinary tract is involved in only 1% of patients affected by endometriosis, and in 85% of these cases affects the bladder ³. For true bladder involvement, the nodule must affect the full thickness of the detrusor muscle. Ureteral involvement is even more rare. It may be bilateral, involving the caudal third along not more than 2cm of the uretero-vesical junction. In urinary endometriosis the symptoms are generally dysuria, hypogastric pain and, if the mucosa is involved, hematuria mostly in concomitance with menstruation ^{3,24}.

A barium enema, intravenous urography and other traditional radiologic examinations involving the use of contrast medium, lack in specificity. MRI and CT scans often fail to solve problems of differential diagnosis from intrauterine lesions, and only transvaginal US and cystoscopy have a greater specificity. However, even these investigations may not provide a definitive diagnosis if the mucosa is intact.

Regardless of the localization – digestive and/or urinary tract – apart from complicated cases requiring laparotomy or emergency laparoscopy, a preoperative diagnosis of extra-gonadal endometriosis is never easy due to disease progression ¹¹.

In practice, only during laparoscopy endometriosis can suggestive lesions be confirmed and other diseases excluded ^{25,26}. At the same time, the female genital apparatus can be studied and, above all, surgical treatment be performed if required by intraoperative findings ²⁷.

Despite the possible, albeit rare, risk of dissemination, laparoscopy should be accompanied by intraoperative histological confirmation, ^{3,13,21} to prevent false negatives and exclude tumors, since failure to recognize the latter situations could lead to unnecessary or inadequate treatment. An excessively demolitive treatment of the former type could only be justified by the rare eventuality of a neoplastic transformation of endometriosic foci.

In particular, the importance of laparoscopy in extragonadal endometriosis lies in the chance of making an early, definitive (using short time frozen section examination), minimally invasive diagnosis.

Surgical acts on gastrointestinal and urinary tract foci,

depending on dimension, range from simple ablation to resection with a maximum extension of 5 cm over the lesion bounds.

Associated genital foci can be treated at the same time and the peritoneum should then be accurately washed at the end of the operation.

Rectal involvement should be treated trough resection any time it's technically possible, to preserve anal canal and sphincter control over defecation.

Rectal ampulla carcinomas, which are very familiar to a general surgeon, require the most demolitive approach available, and the benign nature of endometriosis should motivate the surgeon to be conservative when the terminal rectum is not involved.

For this reason a multidisciplinary approach, involving general surgeons and gynecologists, is desirable in deep pelvis endometriosis.

Procedures shouldn't vary as a result of surgical approach. An endometriosic focus should be treated in the same manner (ablation, resection and so on), regardless of whether the surgeon chooses a laparoscopy or laparotomy.

Moreover, patients affected by extra-genital endometriosis not only benefit from the known advantages of laparoscopic resection in the immediate post-operatory time, but above all show relief of progressive symptoms and sometimes improvement of fecundity.

Another advantage of this technique is the lesser formation of adhesions in a disease, which by its very nature tends to generate this syndrome often requiring a second-look. In 1% of cases the endometriosis is localized at the cutaneous and subcutaneous level ³ and in rare cases the umbilical cicatrix is the primary site. Skin endometriosis can be suspected on the basis of cyclic symptoms, such as pain or bleeding, in concomitance with the menstrual flow, or in the presence of nodules near or on surgical scars or the umbilicus ^{4,5,28,29}.

These lesions are usually assessed by US and MRI, which can reveal hemosiderin and hemoglobin deposits on the endometriosic lesions ^{5,28}. While migration and/or intraoperative contamination of incised tissues by endometrial cells could justify skin or umbilical endometriosis ³⁰, the mechanisms causing endometriosic foci in patients who have never undergone pelvic surgery ^{31,32} and have no suggestive clinical history, are still unclear.

For all skin localizations, surgical resection is the treatment of choice ^{4,28,30} to allow a definitive histological diagnosis. The onset of an adenocarcinoma on endometriosic foci is a rare complication. It was first described in 1925 by Sampson, who listed the essential clinical-morphological criteria for the diagnosis of a malignant transformation of endometriosis ³³.

According to the Author, the demonstration in the same organ of both benign and malignant endometrial tissues, the exclusion of other primary sites and the histological compatibility with a primary endometrial tumor confirm the derivation of a carcinoma from endometriosic foci. However, these criteria are sometimes difficult to apply because typical or atypical endometriosic foci may not be evident, due to destruction by the tumor growth or insufficient sampling 34 .

Moreover, it is extremely difficult to show by histology that it is not a simple concomitance but a true transition from endometriosis to carcinoma, unless there are evident signs lying on the border between the benign and malignant areas ⁷.

The ovary is the most common site for onset of a carcinoma on endometriosis. Many studies have reported ovarian carcinoma associated with ovarian endometriosis, while malignant transformation of extra-ovarian endometriosis, gonadal or not, has been less studied, since it is more rare (79% versus 21%)³⁵.

The most frequent of such sites are the rectovaginal septum, colon rectum and the vagina. While less frequent localizations are the bladder, vulva, lymph nodes, small intestine, umbilicus, retroperitoneum, omentum and pleura ³⁶. The most common histological type of ovarian and extra-ovarian endometriosis, is endometrioid carcinoma. Less common forms include clear cell carcinoma in the colon, rectum, retroperitoneum, bladder, urethra, rectovaginal septum, vulva and on cesarian section scars, 37-39 as well as stromal endometrial sarcoma and carcinosarcoma⁶. Immunohistochemistry can play an important role in the study of such lesions. It can confirm suspected endometriosic foci, especially extra-gonadal, on the basis of CD10 antibodies that are markers of normal but also ectopic or neoplastic stromal endometrial cells. These antibodies show intense staining for stromal endometrial cells. This shows its usefulness especially if cells are few or poorly recognizable on sections stained with hematoxylin-eosin, and can differentiate lesions that could be confused for endometriosis ⁴⁰.

Positivity for CK7 together with negativity for CK20 and CDX2 confirms the endometrial origin in cases of adenocarcinoma on bowel endometriosis, differentiating such forms from the more common bowel adenocarcinoma. Studies of endometrioid adenocarcinomas have demonstrated some chromosomal alterations that are not present in endometriosic lesions. The prevalence of these same alterations in ovarian but not extra-gonadal endometriosic lesions may suggest a precise role of the surrounding ovarian stroma in inducing or promoting a neoplastic transformation ⁴¹. Obviously, this is lacking in other pelvic sites, which have been shown to be rarer localizations of such transformations.

Conclusions

We definitely think that the study on endometriosic pathology is still a rich source of new perspectives. Diagnosis of endometriosis is mostly a matter for gynecologists, because of its indisputable predilection for genital organs.

On the other hand, if a patient shows otherwise inexplicable signs and symptoms, even with a mute anamnesis for gynecological localizations, it's necessary to search for and to treat possible extra-genital foci. A suspect of extra-genital, intra or extra-abdominal, or skin endometriosis, imposes an urgent intraoperative hystopatological examination and the resection of the focus. By these means we can rapidly improve a patient's quality of life and fertility, while at the same time eliminating the risk of malignant transformation.

Riassunto

BACKGROUND: L'endometriosi viene solitamente considerata una patologia esclusivamente ginecologica; diventa, però, di competenza chirurgica quando i foci endometriosici si localizzano in organi non appartenenti alla sfera genitale. Scopo del nostro studio è stato valutare in maniera retrospettiva i casi di endometriosi extra-genitale diagnosticati in un periodo di 10 anni, per un migliore inquadramento della patologia stessa, al fine di evitare procedimenti diagnostici e trattamenti inutili o inadeguati.

METODI: Abbiamo analizzato anamnesi, presentazioni cliniche, diagnosi e terapia chirurgica su un gruppo di 60 pazienti, con età media di 38,2 anni, con endometriosi extra-genitale.

RISULTATI: 1 foci endometriosici a localizzazione intestinale, 37 casi - 61,7% - erano i più frequenti; abbiamo studiato 13 foci (21,7%) della cute, 7 (11,7%) del tratto urinario, in 3 casi (5%), c'è stato un interessamento di più organi pelvici. È importante sottolineare in due pazienti l'insorgenza di carcinoma a partenza da foci endometriosici extra-genitali.

CONCLUSIONI: L'endometriosi extra genitale deve essere considerata come causa di dolore addominale, altrimenti inspiegabile, in giovani donne. Dal momento che le tecniche di imaging mancano di specificità, riteniamo la laparoscopia esplorativa come un potente mezzo diagnostico. Contestualmente, si può procedere all'intervento chirurgico più adeguato, sempre in laparoscopia se possibile, limitando così la formazione di aderenze, che di per sé fa parte della patologia endometriosica e che sarebbe incrementata con la chirurgia open.

Riteniamo infine che l'endometriosi extra-genitale debba essere trattata anche per evitare il raro, ma possibile, rischio di cancerizzazione.

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