Mini Review

CLINICAL INVESTIGATION

Concordance of ulcerative colitis and endometriosis in monozygotic twin sisters: An infrequent but challenging association

Abstract

We describe a rare occurrence of UC and endometriosis in monozygotic twin sisters. The association between endometriosis and IBD assumes a critical clinical relevance due to the overlap of symptoms, making the diagnostic approach as well as medical and surgical therapeutic choices difficult. Furthermore, both conditions have a high risk for surgery, and the need for surgery for one or both diseases requires careful planning strategies. Finally, surgery related to IBD can involve the risk of infertility, which is already present in endometriosis. We collected all cases of endometriosis among our IBD patients and registered bowel disease data (IBD phenotype, age at diagnosis, disease pattern, immunosuppressive or biological therapies), extraintestinal manifestations, comorbidity, and exposure to surgery for IBD. We also calculated the prevalence of endometriosis in IBD patients.

Keywords: Inflammatory bowel disease • Endometriosis • Pelvic surgery • Heritability • Monozygotic twins.

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Abbreviations: Inflammatory Bowel Disease (IBD); Crohn's Disease (CD); Ulcerative Colitis (UC); Magnetic Resonance Imaging (MRI); Genomewide Association Studies (GWAS); Gonadotropin Releasing Hormone (GnRH).

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Introduction

Inflammatory Bowel Diseases (IBDs), including Crohn's Disease (CD) and Ulcerative Colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract [1,2].

Endometriosis is the presence of an endometrium-like epithelium outside the endometrium and myometrium, usually associated with an inflammatory process. Endometriosis can affect various anatomical structures: ovary in the form of cysts (endometrioma), peritoneum (superficial endometriosis), rectum, the sigmoid and ileocecal junction (intestinal endometriosis), districts such as uterosacral ligaments, rectovaginal space, vagina, ureters, bladder in the form of infiltrating nodules often determining a mass effect or fibrosis and abdominal-pelvic adhesions (deep endometriosis); extra-abdominal presentation (cutaneous endometriosis) [3]. Symptoms include chronic abdominal pain, dysmenorrhea, dyspareunia, infertility, and algogenic sensitization. Furthermore, the extent and diffusion of endometriotic implants do not correlate with clinical manifestations, so lesions might not necessarily be considered a disease and, in asymptomatic patients, may be considered a ubiquitous finding [3]. The gold standard for the diagnosis of endometriosis is laparoscopic surgical visualization with histological confirmation; however, endometriomas can be reliably identified by transvaginal ultrasound or magnetic resonance imaging (MRI) [4].

The pathogenesis of endometriosis is still undefined and involves the agreement of endocrine and immunoinflammatory processes. The most accredited theories to explain the origin of ectopic endometrial implants are retrograde menstruation, coelomic metaplasia, and lymphovascular metastatic

spread. The cells that colonize the extrauterine sites are characterized by an abnormal response to hormonal stimuli and are responsible for triggering an inflammatory response in the implant sites and neoangiogenesis and algogenic sensitization phenomena. Hormonal therapies (progestogens, GnRH antagonists) constitute the first line for treating pain and arresting the progression of endometriosis. The surgical option should be considered in case of failure of medical therapy, disease progression, or adhesion syndrome [3].

Materials and Methods

We describe a rare occurrence of UC and endometriosis in monozygotic twin sisters. We collected all cases of endometriosis among our IBD patients and registered bowel disease data (IBD phenotype, age at diagnosis, disease pattern, immunosuppressive or biological therapies), extraintestinal manifestations, comorbidity, and exposure to surgery for IBD. We also calculated the prevalence of endometriosis in IBD patients.

Results and Discussion

A 25-years-old Caucasian female patient with a past medical history of left side colitis was admitted to our hospital because of rectal bleeding and severe abdominal pain. The patient was on maintenance therapy with oral mesalamine. Azathioprine therapy was practiced from the age of 9 to 15 when it was interrupted for sustained remission. Physical examination revealed diffuse abdominal pain. Laboratory examination showed mild anemia and increased C-reactive protein and fecal calprotectin. A pancolonoscopy showed a severe relapse of left side colitis associated with the first finding of substenosis of the sigmoid colon by an extraluminal mass. A trans-abdominal ultrasound revealed a left-side colon wall thickening (6.5 mm) and a left annexial non-vascularized complex mass closely contiguous to the sigmoid colon. The patient was then referred for a gynecological examination, and transvaginal ultrasound and magnetic resonance of the pelvis were performed. She was diagnosed with deep infiltrating endometriosis of the rectovaginal space involving the muscular layer of the sigmoid colon. We conducted a multidisciplinary gynecological and surgical consultation, and conservative treatment was adopted based on colitis left extension and acceptable patency of the colonic lumen. Acute phase therapy for UC was initiated based on oral steroids and, once clinical remission was reached, dienogest hormone therapy was introduced; this therapy was well tolerated with abdominal pain remission. Transvaginal ultrasound performed every six months documented arrest of progression of endometriosis with a reduction in the size of the sigmoid-compressing lesion. Currently, the patient continues hormone therapy and gynecological follow-up.

Her twin sister was also diagnosed with ulcerative proctosigmoiditis when she was five years old. She was on sulphasalazine maintenance therapy after a five-year azathioprine therapy started at age 15 and stopped five years later. Despite the remission of UC, the patient suffered from recurrent abdominal pain, and when she was 24 years old, she received a diagnosis of cystic ovarian endometriosis. She underwent laparoscopic marsupialization of ovarian cysts and adhesiolysis.

The twins did not have a family history of IBD or endometriosis and were not smokers. Both had been on azathioprine treatment before the diagnosis of endometriosis and stopped for sustained remission. In both cases, the diagnosis of UC was made at the pediatric age. The limit of our report is that our patients did not undergo genetic sequencing analyses.

Two cases of colic stenosis have been reported in patients with ulcerative colitis and endometriosis, as in the case of our index patient. In the first case, a 25-year-old patient with an endoscopic finding of sigmoid luminal stenosis during an exacerbation of UC refractory to medical therapy underwent exploratory laparoscopy with a diagnosis of pelvic endometriosis: ileo-pouch-ano-anastomosis and radical excision of the foci of pelvic endometriosis were performed [5]. In the second case, a 39-year-old patient diagnosed with UC and endometriosis had a colonic occlusion with radiological findings of luminal hepatic flexure stenosis extended to the transverse colon and a peripancreatic abdominal mass suggestive of malignancy. However, a CT-guided biopsy of the abdominal mass was diagnostic of endometriosis and the patient was successfully treated with leuprolide and colonic stenting [6]. In both cases, the abdominal symptoms that occurred in patients with UC were attributed to intestinal disease. Therefore, it is crucial to direct the differential diagnosis towards coexisting endometriosis, especially in cases of atypical symptoms or IBD therapy failure.

In our referral center, we retrospectively identified 14 cases of endometriosis and IBD among 1129 women with IBD, with a prevalence of 1.2% (1.9% in UC and 1% in CD). In 7 of 14 cases (50%), the endometriosis localization was ovarian, while in the remaining cases, deep endometriosis was reported. Six out of 14 cases of endometriosis were associated with another disease of the immune spectrum, such as coeliac disease, Hashimoto's thyroiditis, autoimmune hepatitis, and fibromyalgia. All cases of endometriosis in CD were associated with a complicated pattern of bowel disease (penetrating or stenosing). Only in three cases, the diagnosis of endometriosis before that of IBD, while nine patients had received IBD-related surgery before the diagnosis of endometriosis. Seven patients underwent surgery for endometriosis, three of which had one or more IBD surgeries, before the

diagnosis of endometriosis.

According to current hypotheses, the pathogenesis of IBD, although not definitively clarified, is attributable to a combination of genetic and environmental factors; dysfunctions of the immune system, the intestinal barrier, and the microbiome also play a role. Immune alterations involve components of innate immunity that cause adaptive immunity alterations with the activation of cellular pathways responsible for the constitutive activation of the inflammatory phenomenon [1,2]. A recent review reports a positive association between IBD and endometriosis, with an IBD ratio of 2%-3.4% in patients with endometriosis compared to 0.1% in the control groups [7]. An interesting hypothesis from this review is that the risk of IBD in patients with endometriosis may be affected by drugs used to treat endometriosis, such as oral contraceptives or non-steroidal anti-inflammatory drugs. However, many questions remain about the association between the two pathologies, and it is necessary to clarify the weight of genetic and environmental factors in the determinism of both conditions. Endometriosis is an inflammatory disease related to immune dysregulation that affects 10% of women of reproductive age. An increased risk of coexisting autoimmune diseases is described among endometriosis patients but based on low-quality data [4]. The true prevalence of endometriosis is uncertain due to different diagnostic approaches and different population samples considered: 2%-11% among asymptomatic women, 5%-50% among infertile women, 5%-21% among women hospitalized for pelvic pain, and, among symptomatic adolescents, from 49% for those with chronic pelvic pain to 75% for those with pain that does not respond to medical treatment. Epidemiological studies have reported significant family aggregation with concordance in monozygotic twins and 3 to 15 times increased risk of developing the disease for women with first-degree familiarity compared to the general population [3,4]. Several case series reported a concordance in monozygotic twins of 75%-87%, which is higher than the concordance in heterozygous twins or non-twin sisters [8,9].

Before our report, an Australian study evaluated endometriosis in twins, showing a double risk of disease in monozygotic twins compared to dizygotic twins, supporting evidence that the heritability of endometriosis can be estimated at 50% [10]. Some genetic susceptibility loci have been identified in the analysis of germline or somatic mutations of individuals affected by endometriosis. Currently, it is impossible to assess the actual susceptibility provided by these mutations, which constitute a substrate easily affected by unknown environmental factors [4,11,12].

Familiarity is a well-documented epidemiological datum in IBDs, with population studies on twins reporting a 6.3% agreement in twins with UC. Genomewide Association Studies (GWAS), next-generation sequencing studies, and other analyses have identified more than 240 nonoverlapping genetic risk loci, and 30 are shared between CD and UC [1,2]. Although a role of the HLA gene in UC has been proposed [10], conclusive data are lacking, also based on the ethnic heterogeneity of the populations studied, as suggested by Horiya in a case report [13]. Currently, it should be clarified how the susceptibility loci for both pathologies are involved in the pathogenesis of these conditions; it has been shown that the susceptibility genes for endometriosis are included in areas of the genome coding for pathways involved in the immune-inflammatory response: cell adhesion and proliferation, angiogenesis, and pain sensitization [4].

In our report, we described the case of two twins with endometriosis and UC. A cohort study carried out on a large number of Danish women hospitalized with endometriosis analyzed the association with IBD: in comparison with women in the general population, they have a 50% increase in the risk of IBD (SIR=1,5), with a standardized incidence ratio of 1.5 in UC and 1.6 in CD [14].

A case-control study conducted at an American tertiary referral center collected 51 cases with endometriosis and IBD, evaluated the phenotype of IBD and clinical outcomes of patients with concomitant pathologies compared to controls of IBD, and suggested that endometriosis does not impact clinical outcomes of IBD. This report also found that surgically confirmed cases of endometriosis in patients with CD were all associated with a stenosing disease pattern [15]. This data also emerges in our retrospective series. All our patients with CD and endometriosis had complicated bowel disease patterns and underwent at least one surgery for IBD unlike patients with UC and endometriosis, which had less severe disease. However, this finding may depend on the inherent surgical risk of complicated CD, and specific prospective studies with a control population are needed to understand if endometriosis constitutes a significant risk variable.

Conclusion

The association between endometriosis and IBD assumes a critical clinical relevance due to the overlapping of abdominal pain or bleeding symptoms, making diagnostic approaches as well as medical and surgical therapeutic choices difficult. Furthermore, both conditions have a high risk for surgery, and the need for surgery for one or the other or both diseases at the same time requires careful strategies planning. Finally, we must consider that IBD-related surgery can involve the risk of infertility, which is already present in endometriosis.

Since a critical decline in quality of life and socio-occupational functioning can weigh on patients suffering from both pathologies, we aim to conduct

more studies to evaluate the phenotype of IBD, clinical outcome, and risk factors and to clarify the temporal and cause-effect association between these two pathologies.

Acknowledgments

All authors contributed equally.

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Conflict of Interest

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