

Endometriosis and IBD: Two Case Reports and Narrative Review of the Literature

Alessia Dalila Guarino¹, Anna Testa¹, Olga Maria Nardone², Giuseppe Bifulco³, Alessia La Mantia¹, Pierluigi Giampaolino^{4*}, Fabiana Castiglione¹, Miriam Giaquinto¹ and Antonio Rispo^{1*}

¹Gastroenterology, Department of Clinical Medicine and Surgery, School of Medicine, University "Federico II" of Naples, Italy.

²Gastroenterology, Department of Public Health, School of Medicine, University "Federico II" of Naples.

³Gynecology, [^]Department of Neuroscience, Reproductive Sciences and Dentistry; School of Medicine, University "Federico II" of Naples

⁴Gynecology, Department of Public Health, School of Medicine, University "Federico II" of Naples

Corresponding Author

Antonio Rispo, Gastroenterology, Department of Clinical Medicine and Surgery, University "Federico II" of Naples, Italy.

Submitted: 2023, Aug 01; Accepted: 2023, Aug 25; Published: 2023, Sep 01

Citation: Rispo, A., Guarino, A. D., Testa, A., Nardone, O. M., Bifulco, G., et al. (2023). Endometriosis and IBD: Two Case Reports and Narrative Review of the Literature. *Int Internal Med J*, 1(4), 140- 145.

Abstract

Endometriosis is a chronic inflammatory disease caused by the presence of ectopic endometrium-like tissue in extrauterine sites (ovaries, uterosacral ligaments, fallopian tubes or peritoneum), affecting up to 10% of young women.

Clinical manifestations are heterogeneous, varying from asymptomatic to dysmenorrhea, dyspareunia, infertility or chronic pain.

Gastrointestinal (GI) symptoms are reported by patients affected by endometriosis, including abdominal pain, pain during defecation, constipation, diarrhea, nausea, weight loss or obstructive crisis.

Inflammatory bowel diseases (IBD) are a group of idiopathic, chronic disease including Crohn's disease (CD) and ulcerative colitis (UC).

Different Authors suggested an association between endometriosis and IBD, reporting different clinical cases, with different scenarios and outcomes.

Involvement of GI tract can complicate pelvic endometriosis in 3-37% of cases and the differential diagnosis with inflammatory bowel disease (IBD) represents a challenge for the physicians.

Here, we describe two clinical cases of young women affected by IBD associated to endometriosis, underling the importance of differential diagnosis and the impact of these two pathologies on patients' quality of life.

Keywords: Endometriosis, Inflammatory Bowel Disease, Crohn Disease, Endometrium.

1. Background

Endometriosis is a chronic inflammatory disease characterized by the presence of ectopic endometrium-like tissue in extrauterine sites, such as ovaries, uterosacral ligaments, fallopian tubes or peritoneum, and affecting up to 10% of women during reproductive age [1-4].

Clinical presentation may be heterogeneous, varying from asymptomatic to dysmenorrhea, dyspareunia, infertility, or chronic pain [3,5].

Gastrointestinal (GI) symptoms can be reported in endometriosis, including abdominal pain, pain during defecation, constipation, diarrhea, tenesmus, hematochezia, nausea, weight loss or obstructive state in severe forms of the disease [6-9].

Involvement of GI tract complicates pelvic endometriosis in 3-37% of cases and the differential diagnosis with inflammatory bowel disease (IBD) represents a challenge for the physicians [5,8,9].

IBD includes Crohn's disease (CD), ulcerative colitis (UC) and IBD undefined (IBD-U), a group of idiopathic, chronic disease, whose incidence is increasing world-wide [10-13].

They are systemic diseases, with symptoms involving bowel but also extraintestinal organs; extra-intestinal manifestations (EIMs) may present up to 24% of IBD patients, with the need of a multidisciplinary approach and important therapeutic implications [14-16].

Different Authors suggest an association between endometriosis and IBD, reporting different clinical cases, with different scenarios and outcomes [7,8,17].

They share clinical, radiological, histological, and surgical features, with consequences of misdiagnosis or delayed diagnosis, particularly in presence of atypical signs [7,8,17].

Here, we describe two clinical cases of young women affected by IBD associated to endometriosis, underling the importance of differential diagnosis and the impact of these two pathologies on patients' quality of life.

2. Case Report 1

A 38-year-old woman was referred to our Department in 2010, with a diagnosis of coeliac disease on gluten-free diet since 2004. In 2002 she received diagnosis of ovarian endometriosis, so she started estrogen-progestin therapy. In April 2010 she referred diarrhea and abdominal pain; ileo-colonoscopy with biopsies was performed, showing ulcers and erosions in terminal ileum and cecum, suspected for IBD.

Few weeks later, because of bowel obstruction, she underwent urgent ileo-cecal resection with ileo-colonic anastomosis. The histological examination confirmed diagnosis of CD with penetrating behavior associated to intestinal endometriosis. After surgery she started immunosuppressive therapy with azathioprine.

In the following years the patient referred clinical well-being; she continued her gastroenterological and gynecological follow-up; laboratory tests were in range; anti-transglutaminases antibodies were negative.

In 2012, she underwent an ileo-colonoscopy with the evidence of pre-anastomotic recurrence of CD.

In October 2013 trans-vaginal ultrasound and magnetic resonance enterography (MRE) showed the presence of a nodule of endometriosis at the level of sigmoid-rectal junction (Figure 1); she continued estrogen-progestin therapy and Gynecological follow-up.



Figure 1: Magnetic resonance enterography (MRE – T2 sequence) showing the presence of a nodule of endometriosis at the level of sigmoid-rectal junction.

In February 2022 trans-vaginal and trans-abdominal pelvic ultrasounds were performed, showing colliquation signs of bowel localization of endometriosis; she continued hormone therapy, but she also referred diarrhea and rectal bleeding so that she started oral therapy by corticosteroids and topical mesalamine, with good clinical response.

At the time of writing, she is well, continuing estrogen-progestin therapy.

3. Case Report 2

In 2011 a 28-year-old woman was hospitalized in Gynecology Department because of amenorrhea and anemia. A diagnosis of endometriosis was suspected, so that she underwent exploratory laparoscopy, which confirmed ovarian endometriosis. Estroprogestinic therapy was started, with clinical benefits.

One year later, because of the persistence of anemia associated to abdominal pain and diarrhea, the patient was referred to Gastroenterological Department.

Bowel ultrasound, ileo-colonoscopy with biopsies and MRE were performed, showing ileo-colic CD, with ileal sub-stenosis. MRE confirmed the presence of right ovarian endometriotic cyst. Histological examination confirmed the diagnosis of CD and therapy with adalimumab, an anti-tumor necrosis factor alpha (anti-TNF alpha) was started, with clinical benefits.

In October 2015, the patient had clinical recurrence of CD. Thus, MRE and ileo-colonoscopy were performed, with evidence of ileo-colic and entero-mesenteric fistulas. Therefore, in November 2015, she was hospitalized our in Surgical Department and underwent ileo-cecal resection.

In February 2016, 10 months after the operation, ileo-colonoscopy showed the presence of pre-anastomotic recurrence so that adalimumab was reintroduced.

In 2018 the patient got pregnant, so she voluntarily decided to stop therapy with anti-TNF alpha. One year later she referred asthenia, diarrhea, and weight loss; laboratory test showed hemoglobin and C-Reactive Protein (CRP) in range.

Therapy with adalimumab was re-started, with clinical benefit; estro-progestinic therapy was continued.

In 2021 bowel ultrasound, ileo-colonoscopy and MR were performed, showing the disappearance of both pre-anastomotic recurrence of CD and the ovarian endometriotic cyst. At the time of writing, she is doing well and continuing treatment with adalimumab.

4. Methods for Narrative Review

We conducted a computerized Medline/PubMed/EMBASE search using the following key words: endometriosis, Crohn's disease, ulcerative colitis, IBD, inflammatory disease. All pertinent English-language articles were retrieved.

5. Discussion

Endometriosis is a chronic inflammatory disease, characterized by immune dysregulation with proliferation of ectopic endometrium-like tissue in extrauterine sites, affecting affects up to 10% of women during reproductive age [1-7].

Endometriosis may involve ovaries, uterosacral ligaments, fallopian tubes or peritoneum [4]. Observational studies report a prevalence of 8-15 per 1000 in Europe, and an Israelian study recently estimated a prevalence of 10.8 per 1000 among women aged 15-55 years [18].

The etiology is unknown, but according to most accepted etiopathogenetic mechanism, it may be determined by the implantation of endometrium regurgitated from the tubes ("reflux theories") [1-7].

Other possible hypotheses are the metaplastic evolution of celomatic epithelium, that maintains a pluripotential capacity, or the dysregulation of immune system, suggesting the possibility of an autoimmune disease [17].

In a systematic review of 26 population cohort and case-controls studies by Shigesu et al., it has been suggested that endometriosis may be related to different autoimmune disease including IBD, Systemic Lupus Erythematosus (SLE), systemic scleroderma (SS), Rheumatoid Arthritis (RA) and Multiple Sclerosis (MS) [2].

Clinical presentation of endometriosis can vary from asymptomatic to dysmenorrhea (60-70% of cases), dyspareunia (20-35%), infertility (20-30%) or chronic pain, with a wide spectrum of symptoms, in a pathology that may be misdiagnosed for years [5]. GI symptoms can also be found, including abdominal pain, pain during defecation, constipation, diarrhea, tenesmus, hematochezia, nausea, and weight loss. Obstructive symptoms are reported in the severe forms of the disease [1-7]. In some cases, small bowel obstruction may be asymptomatic and diagnosed only with laparoscopic-laparotomic surgery, causing a difficulty in the differential diagnosis with IBD [6,7].

Involvement of the GI tract complicates pelvic endometriosis in 3-37% of cases. More in details, rectosigmoid colon is involved in the 50-90% of patients, rectum in 14%, appendix in 3-18% of cases, and small bowel in the 15% of patients [1-7]. Small bowel localization of endometriosis more frequently involves terminal ileum because of anatomical proximity to ovaries and tubes. It may determine acute and chronic symptoms that represent a real challenge for the physicians [6,8].

Rarely endometriosis give rise to the presence of fistulas or abscesses, with a differential diagnosis with penetrating CD. Bowel endometriosis usually involves subserosa, rarely muscularis propria and sub-mucosa; strictures in endometriosis are caused by smooth muscle hypertrophy [1-7].

Due to serosal or sub-serosal localization of endometriosis, GI hemorrhage is rare, but a cyclic rectal bleeding has been reported in some patients [3].

Appendiceal endometriosis can determine symptoms of acute and chronic appendicitis, with chronic right lower quadrant pain or

cecal intussusception and bowel perforation [1,3,7].

Abdominal mass, occult blood in the stool and annexal mass with deeper nodules with fibrosis are often described in literature. A proper diagnosis of intestinal endometriosis may also be delayed because of misdiagnosis with acute enteritis, diverticulitis, irritable bowel syndrome or neoplasm [1,19].

The gold standard for diagnosis of endometriosis is represented by laparoscopic exploration. Histologic feature of endometrial glands and stroma is a diagnostic finding; tubal metaplasia with ciliated cells or foci of squamous metaplasia are also often observed. Hemosiderin-laden macrophages can be present in the stroma [6,20].

The treatment includes the use of hormonal treatment in order to suppress ovarian activity or surgery to remove ectopic implantation [1-6].

IBD, including CD, UC and IBD-U, is a group of idiopathic, relapsing, chronic disease. CD is characterized by transmural inflammation involving any part of the gastrointestinal tract, while UC involves the rectum with extension into the adjacent mucosa in a continuously way [11-16].

The incidence of these diseases is increasing world-wide, affecting about 2.5 million people in Europe and largely involving young adult population, with significant psychological and social implications [11-16].

The clinical symptoms can be heterogeneous and not always easy to diagnose, including diarrhea, bloody stool, abdominal pain, and weight loss, with a great impact on quality of life of patients [11-16].

IBD are systemic disease, with symptoms involving extraintestinal organs. EIMs may present up to 24% of IBD patients, including skin, joints, or eyes, but may also affect other organs such as the liver and pancreas, with the necessity of a multidisciplinary approach and important therapeutic implications [11-16].

Despite primary conservative therapy for IBD, a notable proportion of patients requires surgery during the course of disease. Approximately up to 20% of patients with UC undergo surgery, whereas up to 70% of patients affected by CD will require surgery. For UC patients, total proctocolectomy with ileoanal pouch anastomosis (IPAA) represents the best surgical approach [11-16].

For CD patients, surgery is not a definitive treatment. Intestinal resection may be performed in patients who are refractory or intolerant to conventional or biological therapies. Moreover, patients who develop severe complications of the disease, such as fistulas, abdominal abscesses, stenosis with recurrent sub-obstructions, will need surgery [13].

Different authors suggested an association between endometriosis and IBD, reporting different clinical cases, with different scenarios and outcomes [1,3,7].

The two diseases share clinical, radiological, histological, and surgical features, with consequences of misdiagnosis or delayed diagnosis, in particular in presence of atypical signs [1-7].

We reported two cases of young women affected by CD associated to endometriosis; all patients underwent surgical resection for CD and one of them was treated with anti-TNF alpha therapy.

These cases illustrate that intestinal endometriosis may mimic and even co-exist with IBD, generating similar clinical symptoms or pathological changes. The differential diagnosis of these two pathologies is a really important issue, since they both involve patients of young age [3].

In our experience, diagnosis of IBD was preceded by a few years by diagnosis of endometriosis, due to the presence of gynecological symptoms, even though different Authors reported in literature that diagnosis of endometriosis may be incidental [5].

In effect, *Craninx et al* reported the coexistence of IBD and endometriosis, evaluating 327 women who underwent surgery for complications related to CD, over an observation period of about 4 years. Eight patients received diagnosis of endometriosis coexisting with CD, basing on the histological evidence of surgical specimen. Differently from our experience, only 1 patient had reported gynecological symptoms, such as dysmenorrhea and dyspareunia, in the absence of cyclic symptoms. In none of these 8 cases, the suspicion of endometriosis had been placed in a pre-operative phase but had been an accidental finding [5].

Moreover, use of oral contraceptives, that represents a usual therapy in endometriosis, as reported in our experience, is related to an enhanced risk of developing IBD, particularly of CD, through the proinflammatory effects of estrogen [18-20]. They have antiapoptotic effects on immune cells, stimulating neo angiogenesis, and promoting B cells. Active estrogen metabolites induce an immunostimulatory activity and influence the synthesis of proinflammatory cytokines. Moreover, the effect of hormonal therapy on bowel microvasculature has been suggested as a possible trigger of mucosal lesions in IBD [18-21].

In our experience we observed that diagnosis of endometriosis was associated to complicated CD, either presence of entero-enteric or entero-mesenteric fistulas, requiring surgery. This finding was reported in different cases in literature, suggesting the hypothesis that endometriosis may be associated with a more aggressive phenotype of bowel disease [1-7].

In particular, *Lee et al* reported a sub-group analysis of 40 patients affected by IBD associated to endometriosis, with evidence of higher prevalence of structuring CD, in whose patients with

surgically confirmed endometriosis [22].

Endometriosis can also determine mucosal distortion that can “mimic” IBD histological damage.

Yantiss reported a study of 44 patients with intestinal endometriosis who underwent surgery. In 11 cases (25%) showed luminal stenosis and 19 cases (42%) showed mucosal evidence of chronic colitis IBD-like, such as crypts distortion, lymphoid aggregate, and fissures [23].

In 2008, Teke described a case-report of a 31-year-old woman with peri-menstrual symptoms of low-grade fever, anorexia, vomiting, abdominal pain and weight loss, diagnosed with endometriosis. She underwent laparotomy because of radiological evidence of small bowel obstruction, with the findings of multiple ileal strictures and fistulas, suggesting a diagnosis of CD. Histological examination of the ileum-colic resection confirmed a diagnosis of IBD, highlighting the difficulty of differential identification of the disease, particularly when a woman in child-bearing age referred cyclical symptoms [1-4].

Guadagno et al evaluated the histological association between CD and endometriosis and determined that in women affected by endometriosis the histological evidence of distortion of crypts or mucosal alteration shouldn't be considered as a diagnosis of IBD, but as a manifestation of endometriosis [1-4].

In a work of Lee et al., 51 patients affected by endometriosis associated to IBD (28 CD/23 UC) were enrolled from tertiary referral centers in a retrospective case-controls study [22].

40 IBD patients had surgically verified endometriosis (78.4%); 21 of them were affected by CD and 19 with UC. Data analysis showed no differences in the risk of pancolitis in UC patients with or without endometriosis; disease localization and behavior of CD was similar between the two groups, also including upper GI localization or the presence of perianal disease [22].

Similarly, there weren't differences in the use of therapies, including anti-TNF or combined therapies.

6. Conclusions

In the process of caring for a patient suffering from IBD or endometriosis, a clinician must be aware of the potential overlap of both diagnoses, in particular when atypical signs or symptoms are present.

Endometriosis coexisting with IBD remains an enigmatic challenging diagnosis in young women.

It's evident the necessity of population-based study to better highlight the associations between these pathologies, in prospective studies with adequate sample size, without confounding data. It would be also desirable to better clarify the pathogenesis of these

diseases, to understand their causes and factors acting as triggers.

Early diagnosis, improvement of diagnostic and therapeutic management and identification of therapies that can best treat both diseases are necessary objectives to fulfill the unmet needs of these diseases.

Funding information: Not applicable.

Conflict of Interests Statement: The authors declare no conflict of interest regarding the current manuscript.

References

1. Jess, T., Frisch, M., Jørgensen, K. T., Pedersen, B. V., & Nielsen, N. M. (2012). Increased risk of inflammatory bowel disease in women with endometriosis: a nationwide Danish cohort study. *Gut*, 61(9), 1279-1283.
2. Shigesu, N., Kvaskoff, M., Kirtley, S., Feng, Q., Fang, H., Knight, J. C., ... & Becker, C. M. (2019). The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis. *Human reproduction update*, 25(4), 486-503.
3. Karaman, K., Pala, E. E., Bayol, U., Akman, O., Olmez, M., Unluoglu, S., & Ozturk, S. (2012). Endometriosis of the terminal ileum: a diagnostic dilemma. *Case Reports in pathology*, 2012.
4. Plummer, P. D., Doorgen, R., Yglesias, B., Phillips, J. K., & Doogan, R. (2022). Acute Large Bowel Obstruction Caused by Endometriosis Requiring Sigmoidectomy. *Cureus*, 14(12).
5. Craninx, M., D'Haens, G., Cokelaere, K., Baert, F., Penninckx, F., D'Hoore, A., ... & Geboes, K. (2000). Crohn's disease and intestinal endometriosis: an intriguing co-existence. *European journal of gastroenterology & hepatology*, 12(2), 217-221.
6. Guadagno, A., Grillo, F., Vellone, V. G., Ferrero, S., Fasoli, A., Fiocca, R., & Mastracci, L. (1959). Intestinal endometriosis: mimicker of inflammatory bowel disease?. *Digestion*, 92(1), 14-21.
7. Chiaffarino, F., Cipriani, S., Ricci, E., Roncella, E., Mauri, P. A., Parazzini, F., & Vercellini, P. (2020). Endometriosis and inflammatory bowel disease: A systematic review of the literature. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 252, 246-251.
8. Teke, Z., Aytakin, F. O., Atalay, A. O., & Demirkan, N. C. (2008). Crohn's disease complicated by multiple stenoses and internal fistulas clinically mimicking small bowel endometriosis. *World journal of gastroenterology: WJG*, 14(1), 146.
9. Popivanov, G., Stoyanova, D., Fakirova, A., Konakchieva, M., Stefanov, D., Kjossev, K., & Mutafchiyski, V. (2020). Ileus caused by small bowel, ileocaecal and rectal endometriosis misdiagnosed as Crohn's disease and managed by synchronous ileocaecal and rectal resection. *The Annals of The Royal College of Surgeons of England*, 102(8), e205-e208.
10. Torres, J., Bonovas, S., Doherty, G., Kucharzik, T., Gisbert, J. P., Raine, T., ... & Fiorino, G. (2020). ECCO guidelines on

- therapeutics in Crohn's disease: medical treatment. *Journal of Crohn's and Colitis*, 14(1), 4-22.
11. Gomollón, F., Dignass, A., Annese, V., Tilg, H., Van Assche, G., Lindsay, J. O., ... & ECCO. (2017). 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *Journal of Crohn's and Colitis*, 11(1), 3-25.
 12. Gomollón, F., Dignass, A., Annese, V., Tilg, H., Van Assche, G., Lindsay, J. O., ... & Gionchetti, P. (2017). ECCO, 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management, *J Crohns Colitis*. 11 (2017) 3–25.
 13. Adamina M, Bonovas S, Raine T, Spinelli A, Warusavitarne J, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, Doherty G, El-Hussuna A, Ellul P, Fiorino G, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gisbert JP, Gomollon F, González Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Kucharzik T, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Stassen L, Torres J, Uzzan M, Vavricka S, Verstockt B, Zmora O. ECCO Guidelines on Therapeutics in Crohn's Disease: Surgical Treatment. *J Crohns Colitis*. 2020 Feb 10;14(2):155-168.
 14. Raine, T., Bonovas, S., Burisch, J., Kucharzik, T., Adamina, M., Annese, V., ... & Doherty, G. (2022). ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *Journal of Crohn's and Colitis*, 16(1), 2-17.
 15. Kaplan, G. G. (2015). The global burden of IBD: from 2015 to 2025. *Nature reviews Gastroenterology & hepatology*, 12(12), 720-727.
 16. Feuerstein, J. D., & Cheifetz, A. S. (2017, July). Crohn disease: epidemiology, diagnosis, and management. In *Mayo Clinic Proceedings* (Vol. 92, No. 7, pp. 1088-1103). Elsevier.
 17. De Souza, H. S., & Fiocchi, C. (2016). Immunopathogenesis of IBD: current state of the art. *Nature reviews Gastroenterology & hepatology*, 13(1), 13-27.
 18. Straub, R. H. (2007). The complex role of estrogens in inflammation. *Endocrine reviews*, 28(5), 521-574.
 19. Cutolo M, Sulli A, Straub RH. Estrogen metabolism and autoimmunity. *Autoimmun Rev*. 2011;11:A460–464.
 20. Wakefield, A. J., Sawyerr, A. M., Hudson, M., Dhillon, A. P., & Pounder, R. E. (1991). Smoking, the oral contraceptive pill, and Crohn's disease. *Digestive diseases and sciences*, 36, 1147-1150.
 21. Chen, M. L., & Sundrud, M. S. (2016). Cytokine networks and T-cell subsets in inflammatory bowel diseases. *Inflammatory bowel diseases*, 22(5), 1157-1167.
 22. Lee, K. K., Jharap, B., Maser, E. A., & Colombel, J. F. (2016). Impact of concomitant endometriosis on phenotype and natural history of inflammatory bowel disease. *Inflammatory Bowel Diseases*, 22(1), 159-163.
 23. Yantiss, R. K., Clement, P. B., & Young, R. H. (2001). Endometriosis of the intestinal tract: a study of 44 cases of a disease that may cause diverse challenges in clinical and pathologic evaluation. *The American journal of surgical pathology*, 25(4), 445-454.

Copyright: ©2023 Antonio Rispo et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.