

Systematic Review

Rare extragenital endometriosis: pathogenesis and therapy

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Abstract

Background: In the context of extragenital endometriosis, the gastrointestinal, urinary tract, abdominal wall, and thorax localizations are considered relatively frequent, while the umbilical, inguinal, sciatic nerve, liver, and pancreas are instead "rare". **Methods:** Online searches were carried out in PubMed database of the last 20 years for these terms: extragenital endometriosis, umbilical endometriosis, inguinal endometriosis, sciatic nerve endometriosis, hepatic and pancreatic endometriosis. The following exclusion criteria were used: (1) Personal surgical history unspecified. (2) Nonspecific histological diagnosis for each type of endometriosis examined. (3) Inability to distinguish between the personal series of the author and the case reports described. (4) Proceedings of scientific meetings were not included. Tables that are easy to consult were compiled. **Results:** 810 titles were found among which 162 studies were selected for reading in full text and finally 114 papers were included, which met the objective of the revision. The so-called "rare" forms of extragenital endometriosis show an unsuspected frequency, an extreme variability of presentation, and uncertain treatment guidelines. **Discussion:** Gynecologists, general surgeons, and neurologists should be well acquainted with these pathologies to avoid confusing diagnostic paths and to set up adequate therapies.

Keywords: Extragenital; Umbilical; Inguinal; Sciatic nerve; Liver; Pancreatic endometriosis

1. Introduction

Extrapelvic endometriosis is a challenging disorder that affects a small percentage of women suffering from endometriosis, approximately 5–8.9%, according to Markham *et al.* [1]. This condition presents with a variety of symptoms depending upon the organ involved and severity of the lesion. According to the literature, locations such the gastrointestinal tract, urinary tract, abdominal wall and thorax are considered "common". Other sites such as the umbilicus, inguinal area, pelvic nerves, liver, and pancreas are considered "rare". Even if these localizations are rare, it is important to know how to recognize them to spare the patient disorienting diagnostic pathways and to be able to establish prompt and effective therapies.

This manuscript aims to provide an overview of what is currently known about this unusual condition and to compare pathogenetic hypotheses and therapeutic choices with prognosis for each of these localizations: umbilical, inguinal, sciatic nerve, hepatic and pancreatic.

2. Materials and methods

Online search was carried out in PubMed database during March and May 2021. The search included a combination of the various term: extragenital endometriosis, umbilical endometriosis, inguinal endometriosis, sciatic nerve endometriosis, hepatic and pancreatic endometriosis. 810 titles were found among which 162 studies were selected

for reading in full text and finally 114 papers were included, which met the objective of the revision: 31 for umbilical endometriosis, 35 for inguinal, 22 for sciatic nerve, 15 for hepatic and 10 for pancreatic. The following exclusion criteria were used: (1) Personal surgical history unspecified and therefore uncertain. (2) Lacking or nonspecific histological diagnosis for each type of endometriosis examined. (3) Inability to distinguish between the personal series of the author and the case reports described. (4) Proceedings of scientific meetings were not included. For each of the investigated locations, we focused on the number of patients presented, the symptoms they complained of, the interventions undergone previously, on the coexistence of genito-pelvic endometriosis, also on the advanced pathogenetic hypotheses and on the follow-up. Table easy to consult were compiled.

3. Objective

The so-called rare forms of extragenital endometriosis are more frequent than previously thought and pose substantial diagnostic difficulties due to the variability of presentation and the diversity of specialists who are primarily involved [1]. In the present review we want to provide a comprehensive and detailed picture of the state of art and discuss the various pathogenetic hypotheses in order to set up rational and articulated therapeutic choices.



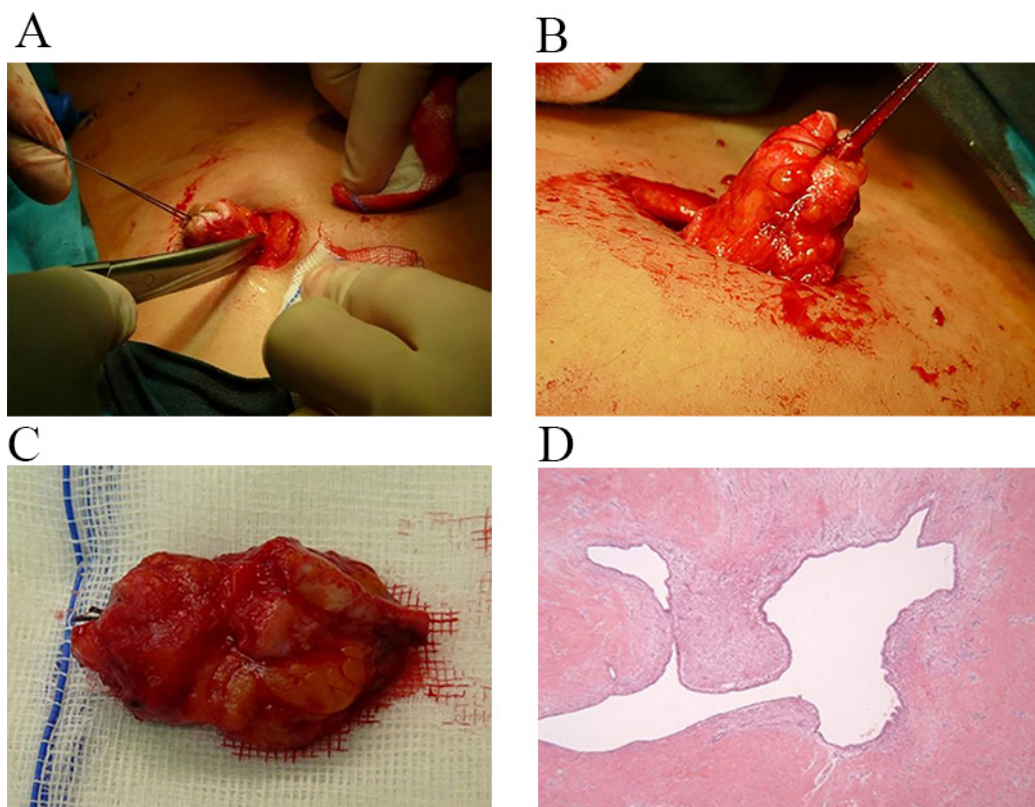


Fig. 1. Radical omphalectomy. (A) periumbilical margin-free incision is performed. (B) The incision is transcutaneously completed to include the fascia and peritoneum. (C) The nodule excised. (D) histological examination confirms the presence of intrafascial endometriosis.

4. Umbilical endometriosis

While the precise rate of prevalence of umbilical endometriosis (UE) is not known, the incidence is estimated to be about 0.5% to 1% of all cases of extragenital endometriosis [2].

The condition can be classified as primary or secondary UE. *Primary UE*, also known as Villar's nodule (after Villar's first description of this scenario in 1886), arises spontaneously with not completely unraveled pathogenetic mechanisms, and it represents nearly 75% of all cases of UE [3]. *Secondary UE* can result from laparoscopic or open surgical procedures with umbilicus involvement.

The pathogenesis of primary UE remains unclear, with different theories proposed by way of explanation. The coelomic metaplasia theory states that endometriosis originates from the metaplasia of pluripotent cells that are present in the mesothelial lining of the visceral and abdominal peritoneum, and the disease may arise from metaplastic changes of urachal remnants, as recently described by Mizutani *et al.* [4]. A second theory suggests that vascular or lymphatic dissemination may be responsible for the presence of umbilical implants [5]. A third theory proposes that hormonal or immunological factors are responsible for stimulating the transformation of normal peritoneal tissue or cells into endometrium-like tissue [6]. Another possibil-

ity involves the funicular cord at birth [7]: after delivery, the resected umbilical cord may be easily contaminated by endometrial cells freed during the stages of childbirth and in those immediately following, with a mechanism similar to that observed and reported in the literature during cesarean sections, laparoscopy, and amniocentesis [8,9].

Both the seeding of endometrial tissue and its direct implantation are recognized as possible causes of secondary UE. The habit of using the umbilicus as a port for laparoscopic access in the abdominal cavity may provide a logical explanation. Moreover, Chatzikokkinou *et al.* [10] hypothesized that the umbilicus, given its unique characteristics of physiologic scar, attracts endometrial cells.

The most typical sign is an umbilical mass or firm nodule whose dimensions can vary from a few millimeters to 5–6 cm. Such lesions can appear brown, blue, or as a faint spot; several authors also describe spontaneous bleeding. The symptoms, such as swelling (90.9%), cyclic pain (81.5%), and bleeding (49.2%), are reported to be more intense during menstruation, but the pain can also be constant. While collecting the anamnesis of these patients, it is common (up to 26% of the cases) to encounter history of dysmenorrhea, dyspareunia, or pain during defecation. The presence of an underlying hernia should be excluded.

Table 1. Patient characteristics, presentation, and treatment of included case reports of umbilical endometriosis.

Author Year	Patients No. (age)	Main symptoms	Previous surgery (Pelvic or abdominal)	Genital/abdominal endometriosis	Main pathogenetic hypothesis	Therapy	Follow-up (months)
Juel J <i>et al.</i> 2017 [18]	1 (33)	Umbilical soreness Dysmenorrhea, dyspareunia	no	yes	NR	omphalectomy	12
Boesgaard-Kjer D, <i>et al.</i> 2016 [19]	10 (28)	Periodic bleeding from umbilicus bulge	no	1 (only 3 LPS)	NR	radical excision + umbilical hernia repair	NR
Calagna G, <i>et al.</i> 2014 [20]	1 (33)	Cyclic umbilical bleeding	no	no	Metaplastic change of urachal remnants	omphalectomy + LPS	6
Claas-Quax MJ, <i>et al.</i> 2015 [21]	1 (27)	Cyclic umbilical bleeding	no	no	Embryonic remnant Coelomic metaplasia	surgical excision	NR
Hoopes K, <i>et al.</i> 2020 [22]	1 (30)	Tenderness, cyclic pain, umbilical pain	Yes: lps cholecystectomy	NR	NR	NR	NR
Bagade, <i>et al.</i> 2009 [23]	1 (35)	Cyclic umbilical bleeding	no	NR	NR	GnRh + Local excision	3
Rzepecki <i>et al.</i> 2018 [24]	1 (44)	Asymptomatic umbilical lesion	Uterine artery embolization	NR	NR	Biopsy No treatment	NR
Genovese G <i>et al.</i> 2018 [25]	1 (42)	Painful umbilical nodule	no	yes	NR	Local excision	NR
Pramanik SR <i>et al.</i> 2014 [26]	1	Cyclic umbilical bleeding and palpable mass	no	no	metaplasia of urachus remnant	Local Excision	6
Nellihela L <i>et al.</i> 2020 [27]	1 (16)	Painful umbilical lump	no	NR	lymphatic dissemination/embryonic remnants	total excision	NR
Ghosh A <i>et al.</i> 2014 [28]	1 (32)	Umbilical nodule with cyclical pain and swelling	no	no	Umbilicus attracts endometrial cells as a physiological scar	total excision	24
Dadhwal V <i>et al.</i> 2011 [29]	1 (42)	Umbilical nodule with cyclical pain	no	no	metaplasia of urachal remnants	Total umbilicus Excision + hysterectomy	16
Kahlenberg LK <i>et al.</i> 2014 [30]	1 (26)	Chronic umbilical bloody	no	yes	NR	NR	NR
Battista R <i>et al.</i> 2009 [31]	1 (32)	Cyclical painful umbilical lump bleeding I	no	no	Müllerian remnants, Haematogenous or lymphatic spread	Total excision	NR
Al-Quorain SA <i>et al.</i> 2017 [32]	1 (31)	Umbilical swelling with intermittent mild pain	no	no	genetic predisposition, immunological defects	Wide excision	6
EğİN S <i>et al.</i> 2016 [33]	1 (28)	Cyclic painful swelling in the umbilicus	no	no	metaplasia of urachus remnants	Total excision	19
Fancellu A <i>et al.</i> 2013 [34]	1 (24)	Cyclic umbilical bleeding and palpable mass	no	no	Embryonic remnants, hematogenous/lymphatic dissemination	Excision of the nodule, saving the navel	24

Table 1. Continued.

Author Year	Patients No. (age)	Main symptoms	Prevoius surgery (Pelvic or abdominal)	Genital/abdominal endometriosis	Main patogenetic hypotesis	Therapy	Follow-up (months)
Taniguchi F <i>et al.</i> 2016 [35]	1 (45)	Catamenial painful umbilical mass	NO	no	lymphatic or hematogenous spreading	Omphalectomy	12
Theunissen CI <i>et al.</i> 2015 [36]	1 (47)	Painful swelling in the umbilicus	no	no	lymphatic dissemination/embryonic remnants	Nodule Excision	2
Boufettal H <i>et al.</i> 2009 [37]	1 (47)	Painful and hitchy umbelical swelling	no	no	Vascular/lymphatic dissemination	Nodule excision	9
Kesici U <i>et al.</i> 2012 [38]	1 (38)	Umbilical lesion with serohemorhagic secretion not cyclic	no	no	NR	Surgical excision	NR
Bonnè E. <i>et al.</i> 2020 [39]	1 (41)	Recurrantly bleeding umbilical nodules	no	yes	NR	Excisional biopsy of the nodules	NR
Bagade PV <i>et al.</i> 2009 [23]	1 (35)	Umbilical nodule bleeding during periods	no	yes	embryonic remnants, coelomic metaplasia	wide local excision of the nodule	NR
Fernandes H <i>et al.</i> 2011 [40]	1 (38)	Blackish nodule	no	yes	metaplasia of urachus remnants	Excision umbilical nodule	12
Capasso L <i>et al.</i> 2020 [41]	1 (45)	Solid umbilical nodule ciclycal increasing	no	no	embryonic remnant, celomic metaplasia	En bloc excision of the nodule along with the overlying skin	60
Van den Nouland D. <i>et al.</i> 2017 [42]	1 (44)	Painless, intermittent dark red discharge from the umbilicus	no	no	coelomic metaplasia, lymphatic or haematogenous spreading	Gnrh for two monhts + omphalectomy	NR
Pandey D <i>et al.</i> 2017 [43]	1 (47)	Cyclic umbilical pain with umbilical swelling	No	yes	NR	Hysterectomy + bilateral adnexectomy	NR
Laferriere N R <i>et al.</i> 2019 [44]	1 (34)	Umbilical bulge and catamenial pain	2 TC	no	surgical scars, especially after C-sections	umbilical hernia repair and resection	NR
Bronfenbrener R <i>et al.</i> 2011 [45]	1 (32)	Cyclical bleeding and umbilical pain	No	NR	NR	NR	NR
Efremidou E <i>et al.</i> 2012 [46]	1 (44)	Umbilical skin lesion accompanied by pain one week before menses	No	no	vascular or lymphatic dissemination, coelomic metaplasia	Surgical excision	36
Paramythiotis D <i>et al.</i> 2014 [47]	1 (46)	Dark-blue hard nodule and pelvic pain	No	no	vascular or lymphatic dissemination, embryonic remnants	Hysterectomy and Umbilical nodule excision	NR

LPS, Laparoscopy; NR, Not reported.

The clinical diagnosis of umbilical endometriosis is challenging due to the fleeting characteristics of the symptoms. Extrapelvic endometriosis should always be considered in the differential diagnosis of an umbilical mass. Other diseases to be excluded are malignant conditions such as melanoma, sarcoma, adenocarcinoma, and lymphoma, as well as benign conditions such as hemangioma, umbilical hernia, sebaceous cyst, granuloma, lipoma, abscess, and urachal anomaly [11]. A delay in diagnosis is common, given the rarity and the elusiveness of this condition. The disease can be silent for a protracted period before making its clinical appearance. The typical imaging modalities applied for the study of the vascularity, size and locations of the lesions are Ultrasounds (US), Computed Tomography Scans (CT), and Magnetic Resonance Imaging scans (MRI). Although the specificity of US for UE is relatively poor, this imaging modality can discern whether the lesion is cystic or solid. Usually, UE appears in the US as a mass of irregular shape situated on the umbilical scar, with ground-glass echogenicity and absent vascularity on the Power Doppler modality. MRI is considered superior for diagnostic purposes, given its more detailed assessment of size, extension and hemorrhagic content of cysts. Moreover, MR imaging offers a more comprehensive view, which can be useful in excluding other abdominal diseases. What is usually seen on MRI is a nodule showing heterogeneous content, with high signal intensity cystic zones. The signal intensity is low on T2-weighted images, while it is intermediate on T1-weighted images [12]. Despite recent technological advances, a recent work from Makena *et al.* [13] demonstrated the adequacy in sensitivity of the clinical examination compared to US, MRI, and CT scans.

This study also showed that these three imaging modalities are almost equivalent [13]. On the other hand, imaging can be helpful in excluding other differential diagnoses with umbilical endometriosis. The initial examination workup is mainly clinical, while histological confirmation represents the final step for a definitive diagnosis. The use of fine-needle aspiration cytology (FNAC) is limited due to the high rate of inconclusive results, reportedly as high as 75% [14]. Furthermore, the risk of seeding and tissue material dissemination should always be carefully evaluated before undertaking such a procedure. Blood serum biomarkers such as carcinoembryonic antigen (CEA) and cancer antigen 125 (CA125) can help in identifying the presence of other endometriosis lesions in the pelvis. Currently, there is no consensus about the next step following a diagnosis of UE. Some studies perform explorative laparoscopies by default, while others advise performing laparoscopy only in cases where the suspicion of intra-abdominal pathology is strong.

The clinical approach to UE may vary. Usually, medical management with hormonal drugs such as oral contraceptives, progestins and gonadotropin-releasing hormone analogues gives relief from symptoms, but only temporar-

ily. After the end of the treatment, it is common to have recurrences of the disease [3]. Although many patients benefit from medical therapy, the best approach appears to be surgery. In fact, excision of the lesion avoids a relapse and the future risk of malignant transformation [15].

Different surgical techniques are described in the literature, ranging from simple excision to radical omphalectomy. Counseling with the patients for a shared decision-making approach is the best option, as some patients prefer not to have their navel operated on, mainly for aesthetic purposes. Primary surgical options include partial omphalectomy and radical omphalectomy. The former consists in the local resection of the endometrial nodule, sparing the umbilicus, while the latter also removes the underlying fascia and peritoneum. This last approach also requires a flap reconstruction of the aforementioned layers. During the local resection of the umbilical endometrial nodule, the surgeon should take care to obtain adequate resection margins. Indeed, the borders of the excision and the integrity of the nodule during the removal are key elements in minimizing local recurrence. Since the literature reports an incidence of simultaneous pelvic endometriosis ranging from 13% to 15%, some authors advocate a concomitant explorative laparoscopy [15]. Conversely, others reserve this surgery only for patients at high risk of pelvic endometriosis. The risk of developing cancer from UE remains relatively low; to date, only two cases of malignant transformation of umbilical endometrioma have been reported. In 1972, Lauslahti was the first author to describe adenocarcinoma of umbilical endometriosis [16].

Obata *et al.* [17] detailed the case of a woman suffering from endometriosis, with a lesion adjacent to a clear cell carcinoma that transformed into a carcinoma from endometriosis at the umbilical lesion. Urachal cancer represents a different disease, generally involving the bladder and the umbilicus. It derives from a malignant transformation of the remaining enteric epithelium in the urachus. The most complete surgical approach consists in an omphalectomy with a concomitant laparoscopic approach [15].

An incision around the umbilicus with excision margins is performed until the fascia is reached. At this point, a Verres needle is inserted through the inferior margin of the incision and adequate pneumoperitoneum is obtained. Then, a 10 mm trocar is inserted through this entrance, along with lateral ancillary ports, including a 10 mm port on the right. The pelvis is accurately examined for endometriosis foci. Eventual lesions are concurrently treated, and tubal patency can be tested with the aid of hysterosalpingography. At the end of the laparoscopic pelvic surgery, the optic is moved into the right axillary access. In this way, a direct vision of the periumbilical tissue is obtained, allowing completion of the incision through the fascia and peritoneum. Finally, the navel is excised en bloc. The peritoneum and fascia are then sutured prior to fixation of the periumbilical skin to the latter. A 2-0 Vicryl absorbable suture is used

for the skin. Following this surgery, the rate of recurrence of UE is low, allowing for an excellent prognosis (Fig. 1; Table 1, Ref. [18–47]).

5. Inguinal endometriosis

Inguinal endometriosis (IE) consists in the presence of endometrial tissue (glands and stroma) in correspondence with the extraperitoneal portion of the round ligament and the surrounding lymphatic and connective structures. As the precise incidence of IE is challenging to assess, especially given the location of the lesions, patients primarily turn to a general surgeon who often make a preoperative diagnosis of another inguinal pathology. Arakawa *et al.* [48] propose a reliable estimate of 0.3–0.6 of all patients with endometriosis, with an nearly exclusive finding in women of childbearing age (peak between 30 and 40 years). In cases subjected to laparoscopy, the simultaneous presence of pelvic endometriosis is almost constant, although cases without evidence of endometriosis are reported.

The pathogenesis of this localization is not always clear. Several theories have been proposed: (1) the implant on the round ligament of endometrial tissue during menstruation; (2) dissemination of endometrial cells by vascular or lymphatic route; (3) activation, under hormonal stimuli, of Mullerian embryonic remains; (4) metaplasia of mesothelial cells. Candiani *et al.* [49] report that more than 90% of cases of inguinal endometriosis were found on the right side. The reasons for this prevailing laterality are located in the clockwise circulation of the peritoneal fluid which drags the endometrial cells, physiologically present in the fluid, towards the right side, while the left inguinal canal is protected by the sigma. Alternatively, it has been hypothesized that the right processus vaginalis in women obliterates later; but this is not proven [50]. However, since in all cases of IE the histological presence of endometriosis on the extraperitoneal portion of the round ligament was highlighted, while in most cases in which laparoscopy was performed, pelvic endometriosis was present at the same time, it seems logical to think that the round ligament is the path of origin of the IE [51].

IE should always be suspected in patients with a painful mass in the groin (especially on the right) that becomes more sensitive and swells in the premenstrual and menstrual period [52]. Instrumental diagnostics (ultrasound, CT) are helpful but not specific; MRI allows one to highlight and stage the concomitant presence of pelvic endometriosis [53], while fine needle aspiration biopsy (FNAB) detects iron in the hemosiderin deposits, typical of endometriosis. [54]. The definitive diagnosis, however, is only post-surgical (biopsy or surgery). In the differential diagnosis, several other conditions must be considered, such as incarcerated hernia, lipoma, granuloma, lymphadenopathies and lymphomas, neuromas, abscess, inguinal canal hydrocele, and subcutaneous sarcoma. The risk of malignant transformation of IE is between 0.7 and

1.0% with 6 cases of cancer reported in the literature. Of those, five out of six were adenocarcinomas, and one was an endometrial stromal sarcoma [55].

Few works in the literature analyze the results of hormonal therapy on IE. Oral contraceptives (OC) alleviated pain symptoms in 1 of 4 patients, while Dienogest was found to be useful in 6 out of 7 cases [56]. The dienogest was also effective in one case in which OC therapy had failed and in one case that relapsed after surgical therapy [57]. Regardless, the gold standard of treatment should be surgery, which is usually able to resolve symptoms and avoid recurrence. However, to be effective and not prone to relapse, surgical therapy must have two requirements: first, it must be accompanied by a thorough exploration of the abdominal cavity and, second, must involve the removal of the extraperitoneal portion of the round ligament. Exploration of the pelvis/abdominal cavity (laparoscopy) is important for highlighting and treating endometriosis present in most cases of IE. Quagliarello *et al.* [58] reports a case of isolated IE, and Moore *et al.* [59] report only one in five cases of IE without concomitant pelvic endometriosis. Majeski also recommends performing laparoscopy along with surgery for IE [60]. As for the surgical technique, it is important to remove all of the extraperitoneal portion of the round ligament, from the inguinal ring to its insertion on the pubic tubercle [51]. The steps of the radical surgery are described as follows: inguinal skin incision between the superior spina iliaca and the pubic tubercle, dissection of the subcutaneous tissue until the identification and isolation of the endometriotic foci, and en bloc removal of the extraperitoneal portion of the round ligament together with the endometriotic and fibrous tissue surrounding. For the reconstruction of the area, the proximal stump of the round ligament is fixed to the fibrous structures of the inguinal canal and a small non-resorbable net is inserted in the inguinal canal. Histological examination generally reveals endometrial glandular structures infiltrating connective tissue and muscle fibers together with a stroma containing hemosiderin.

In conclusion, IE is a rare condition the diagnosis of which requires adequate information and awareness on the part of gynecologists and, above all, general surgeons to whom these patients are most often referred. MRI and FNAB are critical for preoperative diagnosis. Surgical excision, to be effective, must be radical (Fig. 2; Table 2, Ref. [48,51,52,61–92]).

6. Sciatic nerve endometriosis

Endometriosis of the sciatic nerve (SNE) is considered a rare localization of extragenital endometriosis [93], but its clinical relevance is notable for the important consequences that it entails. In some cases, the endometriotic lesions can be clearly identified, in others, they are not identifiable and their nature is suspected on the basis of characteristics of the symptoms and their catamenial cyclicality.

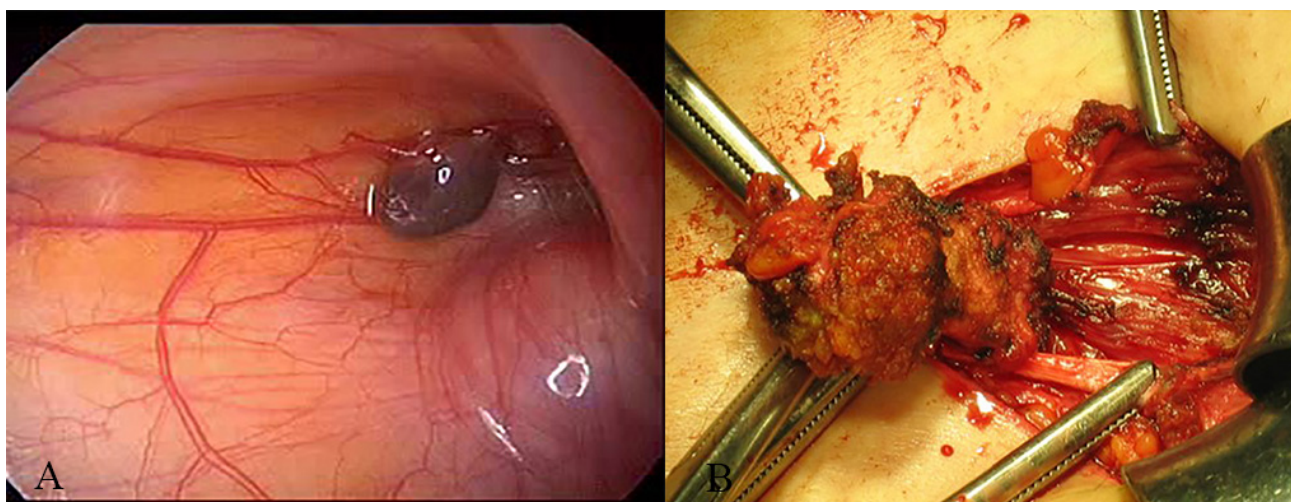


Fig. 2. Inguinal endometriosis of left side. (A) Laparoscopic vision of intrapelvic round ligament endometriosis. (B) Radical extraperitoneal excision of inguinal endometriosis. The pubic periosteum is cleaned, and the round ligament is excised along with the endometriotic tissue.

Recently, however, the refinement of imaging techniques, especially Computed Tomography (CT) and MRI, have reduced the latter cases and made it possible to identify ever smaller endometriotic localizations. SNE can present as a direct extension of a rectovaginal septal endometriosis, but can less commonly be present in isolation, without any apparent endometriosis in the pelvic cavity [94].

The precise pathogenesis of NSE is unclear. Retrograde menstruation with peritoneal seeding is the probable explanation in most cases: from peritoneal implants, the disease can infiltrate the underlying nerve structures. It is common to find peritoneal evagination attached directly to the endometriotic foci of the nerve. Referred to as “pocket sign” [95], this attachment allows the endometriotic tissue to migrate into the nerve structures. This process can occur either during embryogenesis or after retrograde menstruation. The endometrial tissue, once implanted on the nerve, obeys the various physiological cyclical hormones and causes “microcryptomestruations” in the epineurium and perineurium, causing intrafascicular endometriomas and fibrosis [95]. Vercellini *et al.* [96] favor this theory as to the laterality of these lesions: they examined 61 cases of unilateral NSE, comparing the frequency of localization, left versus right. The right side was significantly more involved ($p = 0.007$) than the left. They explain that pelvic peritoneum and the left sciatic nerve are protected from the presence of the sigma by the implantation of endometrial cells. A second theory involving “lymphatic and vascular metastasis” is proposed by Halban [97], who argues that endometriosis arrives in the retroperitoneum and then on the pelvic nerve structures through the dissemination of endometrial cells.

The most common presentation of SNE is sciatica related to menstruation (usually from the second-to-last day of the cycle), with a pain-free period that becomes shorter and shorter with a progressive intensity. Nearly all reported

SNE cases have involved fertile menstruating women; in one case, pain disappeared during pregnancy but returned 6 months postpartum. Pregnancy otherwise had no effect. Pain is usually localized to the thigh and extends down and back to the leg and foot, and is always associated with impaired sensation preceding the pain. Muscle weakness then appears with limb slimming and reflex alterations. The pain is aggravated by coughing, sneezing and straight leg raising (Lasègue’s sign). The ankle jerk is usually depressed or absent. Without diagnosis or treatment, the pain becomes permanent due to the fibrosis that forms on the nerve over time. Patients often resort to narcotic/analgesic for pain relief. Gynecological pelvic examination is generally normal, but in some cases, compression of the uterosacral ligaments reproduced the sciatica pain. Electromyography shows signs of nervous distress via slowing of conduction speed and is very useful for excluding root compression and for monitoring nerve recovery in the follow-up.

MRI is the best imaging method for diagnosing Sciatic Nerve Endometriosis (SNE). Endometriotic foci exhibit high signal intensity on T1 images and low or high signal on T2 images, depending on the stage of lesions as well as the stage of period [98,99]. Unfortunately, not all cases of SNE can be identified on MRI [100]; nevertheless, it is an important investigative test that will rule out other potential etiologies. Many other neurological and orthopedic pathologies can enter into differential diagnosis: spondylotic nerve root compression, hip joint arthritis, lumbar disk disease, arachnoiditis, primary neural tumors, metastases, gluteal artery aneurysm. Due to diagnostic difficulty, a multidisciplinary team approach including neurosurgical and orthopedic involvement is often necessary.

Table 2. Patient characteristics, presentation, and treatment of included case reports of inguinal endometriosis.

Author Year	Patients N (median age)	Prevalent symptoms	Pelvic/Abdominal endometriosis	Previous surgery	Main pathogenetic hypothesis	Therapy	Follow-up
Fedele L, <i>et al.</i> 2007 [51]	5 (36)	Catamenial inguinal pain, paresthesia in the right thigh	100% pelvic	All patients had first-line inguinal surgery with recurrence of symptoms	NR	Radical Surgical excision	5–12 years: Symptoms resolution
Jorge-Moreira C <i>et al.</i> 2016 [61]	5 (32.8)	Catamenial painful, non reducible, hard inguinal mass	No	1 patient: 2 CS 1 patient: 1 CS	Vascular/lymphatic spread, metaplasia mesothelial cells	3 Surgical excision 1 Surgical excision + EP 1 EP	Symptoms resolution
Wolfhagen N <i>et al.</i> 2018 [52]	9 (32.5)	Swelling and cyclic pain the groin in 3 patients	1 pelvic end.	No	retrograde menstruation; persistent processus vaginalis	Open excision without mesh	6 years: no recurrence
Basnayake O <i>et al.</i> 2020 [62]	1 (27)	Painless, right inguinal swelling	No	No	NR	Complete excision of the cyst	12 months: no recurrence
Fujikawa H <i>et al.</i> 2020 [63]	1 (42)	Right groin pain	No	No	NR	Wide excision	No recurrence
Fong KNY <i>et al.</i> 2019 [64]	1 (42)	Right groin swelling	No	No	Metaplasia of coelomic mesothelial cells	Incision of the mass and drainage	NR
Ion D <i>et al.</i> 2017 [65]	1 (42)	Painful bulging mass in the right groin	No	No	endometrial cells extended through the deep inguinal ring	Wide excision of the nodule	4 months: no recurrence
Milam MR <i>et al.</i> 2006 [66]	1 (47)	Persistent and enlarged right groin mass	Yes (severe)	Hysterectomy and bilateral adnexectomy	NR	Wide excision	12 months: adenocarcinoma arising in endometriosis
Mu B <i>et al.</i> 2021 [67]	3 (36)	Inguinal mass with catamenial pain 2 patients (ovarian-pelvic) (1 left side, 1 right, 1 bilaterally)	2 patients (ovarian-pelvic)	2 patients op for endometriosis	NR	Round ligament excision and pelvic endometriosis ablation	84.6 months: No recurrence, all patients developed adenomyosis
Stojanovic M <i>et al.</i> 2013 [68]	1 (40)	Growing subcutaneous nodule and cyclical pain in the right inguinal region	Nr	Myomectomy	NR	Excision of endometriosis in the cutaneous scar	12 months: no recurrence
Kapan M <i>et al.</i> 2003 [69]	3 (44)	Lump and catamenial pain in the groin (2 right, 1 left)	No	Nr	retrograde menstruation, vascular/lymphatic spread, or coelomic metaplasia	Excision of the lesions with a part of the round ligament	No recurrence
Husain F <i>et al.</i> 2015 [70]	1 (32)	Lump and cyclical pain in the right groin	No	1 CS	retrograde menstruation; vascular/lymphatic spread	Excision of firm fibrotic tissue.	15 months: no recurrence

Table 2. Continued.

Author Year	Patients N (median age)	Prevalent symptoms	Pelvic/Abdominal endometriosis	Previous surgery	Main pathogenetic hypothesis	Therapy	Follow-up
Apostolidis S <i>et al.</i> 2009 [71]	3 (38)	Cyclic discomfort in the inguinal region (2 right, 1 left)	1 case yes	Case 3: endometriosis	NR	Excision of mass adherent to the round ligament	NR
Kiyak G <i>et al.</i> 2010 [72]	1 (42)	Right groin hernia	No	2 CS	Retrograde menstruation through the deep inguinal ring	Hernia repair (focal endometriosis detected) + E/P	3 months: No recurrence
Thomas JA <i>et al.</i> 2020 [73]	1 (23)	Swelling and pain in the right groin	No	No	NR	Excision biopsy of the swelling	NR
Chalouhi GE <i>et al.</i> 2007 [74]	1 (25)	Painful right inguinal swelling, increasing around menses	No	Appendectomy	NR	Total surgical excision of the mass	30 months: no recurrence
Mourra N <i>et al.</i> 2015 [75]	42 (35)	Groin lump, periodic menstrual tenderness (11 left side, 29 right, 2 unknow)	5 patients had a prior history of endometriosis	No	Retrograde menstruation	Wide excision of the inguinal lumps	In 14 patients: 1 recurrence after 3 years
Sumter DB <i>et al.</i> 2012 [76]	1 (45)	Inguinal left groin bulge progressively increased in size	No	No	Retrograde menstruation; vascular or lymphatic spread	Excision of the cyst	12 months: no recurrence
Albutt K <i>et al.</i> 2014 [79]	1 (23)	Sudden protrusion in her left groin, associated pain	No	No	NR	Excision of a left inguinal hydrocele and repair with mesh + EP	Newly documented endometriosis.
Jena SK <i>et al.</i> 2020 [77]	1 (25)	Painful persistent mass in the right groin	Nr	Nr	direct extension of endometriosis on the round ligament	Wide surgical excision	NR
Kim DH <i>et al.</i> 2014 [79]	1 (40)	Painful mass in the right inguinal area, increasing during menstruation	Nr	No	retrograde menstruation; vascular/lymphatic spread	Wide surgical excision, including the extraperitoneal portion of the round ligament	At 2 months, complete recovery
Azhar E <i>et al.</i> 2019 [80]	1 (33)	Right groin pain, with a tender lump	Ovarian endometrioma	CS + op. For endometriosis	retrograde menstruation or vascular/lymphatic spread	Open hernia repair surgery	At 10 days, complete recovery
Honl R <i>et al.</i> 2019 [81]	1 (24)	Hard, sensitive lump in the left groin	Pelvic endometriosis	LPS for endometriosis.	trans-tubal regurgitation, venous or lymphatic spread	Hormonal therapy	NR

Table 2. Continued.

Author Year	Patients N (median age)	Prevalent symptoms	Pelvic/Abdominal endometriosis	Previous surgery	Main pathogenetic hypothesis	Therapy	Follow-up
Pandey D <i>et al.</i> 2015 [82]	1 (39)	Left-sided irreducible, tender mass, with catamenial pain	No	CS	extension of endometrial tissue along the right round ligament	In toto removal of the endometrioma, extending up to round ligament	Asymptomatic
Licheri S <i>et al.</i> 2003 [83]	1 (29)	Roundish lump in the inguinal region and cyclical pain	No	Nr	NR	En-bloc removal of the lump and the inguinal segment of the round ligament	No symptoms at 3 months
Boggi U <i>et al.</i> 2001 [84]	2 (32.5)	Painful mass in the right groin, increasing during menses	No	Case 1: CS	NR	Open surgery with hernia reduction	Asymptomatic
Terada S <i>et al.</i> 2006 [85]	1 (24)	Tumor mass in the right side of the pubic region, with increasing pain	No	Nr	Retrograde menstruation, coelomic metaplasia	Excision of the mass and part of the round ligament	No recurrence
Jimenez <i>et al.</i> 2011 [86]	1 (35)	Painful tender groin mass, catamenial pain	No	Right nephrectomy	Coelomic metaplasia	LPS excision of the cyst and repair with mesh	NR
Rajendran S <i>et al.</i> 2012 [87]	1 (36)	Lump in the left groin, with occasional pain	No	Hysterectomy (fibroids)	Coelomic metaplasia	Patient refused surgery	NR
Prabhu R <i>et al.</i> 2013 [88]	1 (49)	Swelling in the left groin	No	CS	non-obliteration of the parietal peritoneum	Surgical excision of the round ligament cyst	Asymptomatic
Kaushik R <i>et al.</i> 2008 [89]	1 (37)	Swelling in the right inguinal region with associated pain	No	CS	tubal regurgitation, patency of the Nuck's Canal	LPS lump excision	NR
Wong WS <i>et al.</i> 2011 [90]	1 (48)	Right inguinal mass and pain during the menses	No	No	direct implantation	Excision of the groin mass	NR
Arakawa T <i>et al.</i> 2019 [48]	20 (37.2)	13 patients: painful right inguinal mass 5: painful left inguinal mass 2: painful bilateral inguinal mass 16 cases referred symptoms association to menstruation	No	15 patients: no surgery 5 patients: abdominal surgery	coelomic metaplasia, tubal regurgitation and lymphatic spread	En bloc resection + E/P	1 case of postoperative relapse required hormonal therapy
Ducarme G <i>et al.</i> 2007 [91]	1 (28)	Right painless inguinal nodule	No	1 CS Inguinal hernia	NR	Wide excision With hernia repair	1 year: Complete recovery
Wang CJ <i>et al.</i> 2009 [92]	1 (35)	Tender mass in left groin, cyclically exacerbating	No	No	Retrograde menstruation; patency of the Nuck's canal	Surgery + gnrh agonist	12 monts: No recurrence

NR, Not Reported; CS, Cesarean Section.

Treatment of Sciatic Nerve Endometriosis (SNE) depends on the severity of symptoms and the reproductive desires of the patient. The only permanent cure is accomplished by surgical menopause (bilateral oophorectomy), which may be considered when reproductive function is not an issue, symptoms are severe, or when conservative methods have failed. In young patients, on the other hand, hormonal therapy to suppress gonadal activity allows confirmation of the diagnosis and prevents the disease from progressing. However, hormone therapy must be continued for an extensive duration, does not allow the onset of pregnancy, and has a considerable risk of relapse upon suspension [101]. In advanced cases, even after complete surgical removal of the lesions, complete resolution of the symptom—especially of the motor deficit—is unlikely, leading us to believe that the prognosis in ENS essentially depends on the period of time elapsed between the onset of symptoms and the initiation of therapy [102].

Some authors have supported the systematic surgical exploration of the affected sciatic branches. This approach has several advantages. First, it allows the histological confirmation of the diagnosis of endometriosis, or of other pathological conditions such as metastatic neoplasms or neurogenic tumors. Possover *et al.* [93] have long supported the use of laparoscopy for this purpose. There are two main methods of accessing the retroperitoneal pelvic nerves: the midline approach, starting from the sacral promontory and traversing the hypogastric fascia, and the lateral approach which is performed by retracting the external iliac vessels to expose primarily somatic nerves. Central nerve lesions, on the other hand, require a mixed approach, both midline and lateral. Ceccaroni *et al.* [103] emphasize the importance of dissecting and identifying the structures before excision of disease to minimize the risk of injury to the neighboring neurological structures. This retroperitoneal neuroanatomical knowledge requires specific expertise. Possover *et al.* [104], based on his extensive pioneering work, has established a unique surgical pelvic discipline called neuropelveology, which must be conducted primarily, he argues, by gynecologists who are more familiar with complex laparoscopic surgery for pelvic endometriosis.

In conclusion, neuropathies and radiculopathies related to endometriosis are much more common than previously believed. Faced with sciatic pain in a young woman with menstrual recurrence, the diagnosis of endometriosis must always be considered. The prompt adoption of hormone therapy to suppress gonadal function allows confirmation of the diagnosis, blocks the progression of the disease, and often avoids inappropriate neurosurgical procedures which in themselves can cause permanent neurological damage (Table 3, Ref. [93,99,100,103,105–121]).

7. Hepatic endometriosis

Hepatic endometriosis was first described by Finkel *et al.* in 1986 [122]. It is a very rare condition characterized by the presence of endometrial tissue (stroma and glands) in the liver. Only a few cases are reported in the literature and the diagnosis is challenging for its variable appearance on imaging and the need for histological findings [123]. HE is found more often in patients with severe abdominal/pelvic endometriosis, while its incidence is higher in the right hepatic lobe. This asymmetrical lateral distribution is likely attributable to the clockwise circulation of the peritoneal fluid that goes from the pelvis to the upper abdomen (liver and diaphragm). Breathing movements and intestinal peristalsis both favor this process [124]. A second theory on the pathogenesis of HE is that of coelomic metaplasia [125]. The peritoneum has a high metaplastic potential: it transforms into endometrial tissue under the influence of various stimuli and thus the epithelium covering the surface of the liver becomes endometrial tissue and invades the liver parenchyma. A third theory involves lymphovascular spread which explains cases in which hepatic endometriomas are only intraparenchymal [126]. A last theory is that of survival of the intrahepatic Mullerian rest: the Mullerian structures believed to be in the hepatic parenchyma maintain their functional potential, even surviving the long hormonal silence between the fall of placental hormones and the onset of puberty [127,128]. As regards the rare cases of postmenopausal HE, it is thought [128] that they may be linked to the reactivation of endometrial implants following the administration of hormone replacement therapy in patients with previous history of endometriosis.

Most patients with HE are symptomatic, with abdominal pain generally localized in the right upper quadrant (RQU), whereas only few patients have no symptoms and are occasionally diagnosed for the presence of a liver mass. In rare instances, the abdominal pain is catamenial and entail nausea and vomiting. Objective examination revealed a hepatic palpable mass in some patients accompanied by ascites and mild jaundice; alteration of liver function was present in few cases. There are no specific serological markers that can differentiate endometriosis from other liver lesions. In cases of HE undergoing FNAB, some results revealed endometrial tissue, but also findings such as necrotic and inflammatory tissue [129].

The lesions of HE can be highlighted with Ultrasound, CT and MRI, but there are no pathognomonic findings of these investigations for the diagnosis of Hepatic Endometriosis (HE). Accordingly, histopathologic examination is considered the gold standard for definitive diagnosis. The most common imaging features of HE seen in the reported cases are “well defined lobulated cystic lesions with solid components and septations” [130].

Table 3. Patients characteristics, presentation and treatment of included case reports of SNE.

Author	Cases	Prevalent symptoms	Time	Abdominal/pelvic endometriosis	Previous surgery	Pathogenetic hypothesis	Terapy	Follow-up
Year	N. (mean age)							
Hettler A, <i>et al.</i> 2006 [105]	1	Right foot-drop, sensory disorder, atrophy of the gluteus		Yes		Compression	Desogestrel + Surgical excision	>15 months
Arànyi Z <i>et al.</i> 2016 [106]	2 (48)	1: catamenial pain radiating from the right gluteal region to the foot 2: severe sciatica on the left side, and a progressive weakness of dorsiflexion of the left foot ensued	1: 15 months 2: 7 years	1: no 2: yes, previous ovarian cyst	1: no 2: ovarian cystectomy	Perineural spread from the gluteal region	1: triptorelin + long term dienogest 2: dienogest	1: 6 months, pain relief 2: NR
Fedele L <i>et al.</i> 1999 [100]	3 (35)	Case 1: dysmenorrhea and catamenial left-sided sciatica. 2: left severe pelvic pain with catamenial sciatica 3: catamenial right sciatica and partial footdrop since 2 years.	1: 3 years 2: 3 months 3: 8 years	Yes	1: explorative LPS	NR	Leuprolide acetate + transdermal E2, 25 mg daily	1: 10 months sympyoms free 2-3: 12 months, partial recovery
Lomoro P <i>et al.</i> 2019 [99]	1 (36)	Sharp right-sided low back pain radiating to right lower extremity	NR	No	No	Intra- peritoneal seeding with subsequent nerve compression	Nerve-sparing laparoscopic surgery, with resection of the blood containing-cyst	6 months, no recurrence
Saar TD <i>et al.</i> 2018 [107]	1 (24)	Progressively worsening right hip and buttock catamenial pain	6 months	No	No	Direct extension of deeply infiltrative rectovaginal disease	Nerve sparing laparoscopic excision + IUD insertion + 6 monthly goserelin + Norethisterone	36 months, no recurrence
Possover M 2017 [94]	46 (28)	Impossibility to stand on tip-toes. All patients suffered from inconstant sciatic pain	NR	No	No	NR	Laparoscopic surgery, with different degrees of sciatic nerve excision	60 months, total functional recovery
Floyd JR <i>et al.</i> 2011 [108]	1	Intermittent right buttock pain extending along posterior thigh and calf to the sole of foot	5 years	No	Removal of an intradural mass	Perineural and intraneural invasion and external compression	Open decompressive surgery with partial resection of the piriformis muscle + leuprolide acetate	24 months, partial relief

Table 3. Continued.

Author Year	Cases N. (mean age)	Prevalent symptoms	Time	Abdominal/pelvic endometriosis	Previous surgery	Pathogenetic hypothesis	Terapy	Follow-up
Mannan K <i>et al.</i> 2008 [102]	1 (25)	Constant tight pain from the left buttock, increasing in severity during menstruation.	2 years	No	No	Peritoneal diverticulum allowing endometrial tissue to migrate into the sciatic	Microsurgical cystectomy with nerve sparing	12 months, partial relief and regained functionality
Capek S <i>et al.</i> 2016 [110]	1 (45)	Cyclic left hip pain, with posterior dyesthesias, weakness in left foot dorisflexion	5 years	No	No	Perineural spreading	Laparotomy and total abdominal hysterectomy with bilateral salpingo-oophorectomy and neurolysis	7 weeks, pain relief
Richards BJ <i>et al.</i> 1991 [111]	1 (46)	Painless right foot drop, with numbness and tingling	20 months	Yes	No	NR	Left salpingo-oophorectomy, with drainage of the left endometrioma.	24 months, asymptomatic
Dhote R <i>et al.</i> 1996 [112]	1 (30)	Right sciatica, with pain, increasing during menstruation	>6 months	Yes	Left salpingo-oophorectomy	NR	Surgical excision of the compressing cyst + gnrh agonist for 6 months	12 months ,asymptomatic
Teixeira AB <i>et al.</i> 2011 [113]	1 (26)	Intense pain and weakness in the lower left limb	9 years	No	No	Nerve damage due to cyclic inflammation of the ectopic tissue in the epineurium and perineurium	Microsurgical exeresis of a cystic lesion in the left sciatic nerve	Asymptomatics
Possover M 2007 [94]	3 (30)	Right sided sciatica/neuralgia	Case 1: 3 years	Case 1: no	Case 1/2: No	Neuropeptide Y-sympathetic nerves may induce neoangiogenesis and promotegrowth of extraperitoneal endometriosis	1: LPS nerve sparing excision of the lesion 2: dissection of the endometriotic tissue compressing the sciatic nerve 3: neurolysis of the sciatic. Obturator and pudendal nerves	1: 1.5 years
			Case 2: 7 years	Case 2/3: yes	Case 3: gluteal neurolysis of the sciatic nerve			2: 5 months
			Case 3: 9 years					3: 4 months
Papapietro N <i>et al.</i> 2002 [114]	1 (29)	Back pain radiating to right thigh, worsening during menstruation	2 years	No	No	NR	Neurolysis of the sciatic nerve	Asymptomatsc, no recurrence 16 months, no recurrence
Descamps P <i>et al.</i> 1995 [115]	1 (39)	Episodic pain in the back and left leg	3 years	No	No	Peritoneal diverticulum permitting endomet al tissue to migrate to the sciatic nerve	Cyst excision and sciatic nerve neurolysis + gnrh agonist × 3 months + Promegeston 0.5	5 months, neurological recovery

Table 3. Continued.

Author Year	Cases N. (mean age)	Prevalent symptoms	Time	Abdominal/pelvic endometriosis	Previous surgery	Pathogenetic hypothesis	TeraPy	Follow-up
Jiang H <i>et al.</i> 2014 [116]	1 (31)	Catamenial left gluta pain, radiating to the thigh	2 years	No	No	Lymphatic dissemination from the principal focus	Gestrinone × 8 months + laparoscopic transgluteal excision of the endometrioid tissue and neurolysis of the sciatic nerve	9 months, no pain but no improvement in neuromuscular deficit
Yanchun L <i>et al.</i> 2019 [117]	1 (20)	Pain and numbness in left lower limb, not associated to menstruation	6 years	Yes: severe dysmenorrhea	No	Peritoneal diverticulum permitting ectopic endometrial tissue to migrate to the sciatic nerve;	Transabdominal and transgluteal cyst excision	5 years, asymptomatic
Carrasco AL <i>et al.</i> 2017 [118]	2 (37)	Case 1: left sciatica Case 2: low back pain radiating to buttock and right leg	Case 1: 8 years Case 2: 5 years	Case 1: no Case 2: yes	No	Perineural spreading	LPS excision and: case 1: removal of the left uterosacral ligament Case 2: neurolysis + dienogest2 mg/ethinylestradiol	Case 1: 4 years, symptoms free Case 2: persistent symptomatology
Ceccaroni M <i>et al.</i> 2011 [103]	1 (41)	Right sciatica and foot drop, dysesthesia, and paresthesia in the ischiatic region worsening during menstruation	3 years	Yes	No	Lymphatic and vascular metastasis and neural theory	LPS nerve-sparing eradication of deep pelvic endometriosis, with right lateral parametrectomy + neurolysis	18 months, disease free
Siquara de Souse AC <i>et al.</i> 2015 [119]	2 (40.5)	Case 1: low-back pain radiating to buttock Case 2: catamenial low-back, hip, and right lower-extremity pain	2 years	No	Case 1: no Case 2: LPS for pelvic endometriosis	Perineural spread	Case 1: hormonal therapy Case 2: Gn-RH agonist	Case 1: 6 months, symptoms resolution Case 2: 5 years, mild residual pain
Pham M <i>et al.</i> 2010 [120]	1 (39)	Gluteal pain radiating to right dorsal thigh peaking during menstruation	4 years	Primary infertility	Diagnostic LPS + myomectomy	NR	External neurolysis of the sciatic nerve + leuprolide acetate	3 months, persistent neurological impairment
Decesare SL <i>et al.</i> 1995 [121]	1 (33)	Right buttock and sacral pain, radiating to the posterior aspect of the leg	4 months	Yes	Diagnostic LPS	NR	Leuprolide 3.75 mg + LPS hysterectomy and bilateral salphingo-oophorectomy +	2 weeks, asymptomatic

NR, Not Reported; LPS, Laparoscopy.

The clinical and instrumental diagnosis of HE is extremely difficult and thus diagnostic confirmation can only be obtained from surgical findings. The pathologies that can enter into differential diagnosis with HE include: hemangioma, hematoma, abscess, echinococcal cyst, secondary oncological lesions. HE should always be considered when a patient presents with a liver mass both in childbearing age and in menopause, even without a history of endometriosis.

The treatment of HE is far from being standardized because its natural history is unknown and there is a lack of prospective studies on its evolution. However, although malignant transformation is rare, surgery remains the treatment of choice. Two cases of hepatic adenocarcinoma originating from endometriotic lesions have been described in two women aged 52 and 54, without recurrence after removal of the lesions [131]. If the patient has symptoms, surgical treatment is mandatory, but even if there are no clear symptoms, surgical treatment is recommended to avoid complications that can occur when lesions deepen into the liver parenchyma. A hormonal treatment of HE has been proposed, with progestogens, danazol and GnRH agonists [132], but even if the symptoms are reduced, the side effects and long-term risks of these treatments remain. Eychenne *et al.* [133] reported medical treatment with aromatase inhibitors in postmenopausal patients as the lesions were not surgically attackable. Prodromidou *et al.* [123] analyzed data regarding 31 patients with HE following operation. In 14 (45.2%) cases, a cyst excision was performed, while in the remaining 17 cases, a more extensive hepatic resection (minor or major hepatectomies) was performed. The excised cystic lesions contained clear or chocolate colored liquid. Intraoperative histological examination with a diagnosis of endometriosis was performed in five cases. The postoperative hospital stay was from one to 13 days. There were no complications except for one case with bile loss. In one case reported by [134], there was a recurrence of endometriosis 18 years after the operation. No cases of intra- or postoperative death were reported in the studies reviewed.

Except in few instances, all patients with HE in the literature were operated on by laparotomy. The laparoscopic approach is used in selected cases [135], with the advantages of an easier and more complete inspection of the entire abdominal cavity, the opportunity to simultaneously treat other endometrial localizations and to avoid unnecessary laparotomy in case of extensive carcinomatosis.

In conclusion, HE is a rare pathology whose diagnosis is difficult due to the lack of clinical and instrumental pathognomonic findings; however, it is considered in the differential diagnosis of hepatic diseases, especially in women of childbearing age with a prior history of pelvic endometriosis. The most convenient therapy is surgical, and the type of surgery depends on the extent of the lesion and its localization (Table 4, Ref. [133,136–149]).

8. Pancreatic endometriosis

PE is extremely rare: the first case was presented by Machevski *et al.* [150] in 1984; subsequently, only a few other cases have been reported in the medical literature. Diagnosis is often only postsurgical, and affected women can be both reproductive and postmenopausal [151].

The pathogenesis of PE is not entirely clear: plausible theories include menstrual endometrial implantation, the hematogenous/lymphatic dissemination and coelomic metaplasia. PE is associated generally with symptoms such as chronic or acute abdominal pain (pancreatitis), involuntary weight loss, and digestive difficulties. The localization of pain is generally epigastric and predominantly on the left. Only in half of the cases described in the literature does the pain have a catamenial recurrence and only very few times has the diagnosis or at least the suspicion of PE been made before the surgical finding. Most of the reported cases are described in reproductive age [152], but one case was found randomly in a 63-year-old patient [153]. Acute symptoms may be due to spontaneous rupture of pancreatic endometriomas [154].

There are no clear clinical or imaging criteria for establishing the endometriotic nature of a pancreatic cyst which differentiates it from other cystic lesions of the pancreas; in almost all reported cases, the diagnosis was postoperative. Generally, pancreatic endometriomas are localized in the tail; those in the body are rarer. They can be both solitary and multiple. No typical imaging features have been established for PE. There can be highlighted cystic formations of variable volume, with inconstant hemorrhagic aspects; in one case [155], is described a solid nodular component. Serological diagnostic (CA19.9) has not been shown to be useful for PE, unlike other pancreatic lesions.

Under ultrasound, PE is highlighted as small cystic hypoechoic lesions with a simple or complex content. The fine needle aspiration biopsy (FNAB) under ultrasound guidance may be useful to clarify the diagnosis in doubtful cases, but some authors have reported [156] the possibility that the needle may spread the lesions, as in cases of Intraductal Papillary Mucinous Neoplasia (IPMN) where pseudomyxomas are formed.

MRI in PE generally shows mixed lesions, partly serous and partly hemorrhagic. While it is true that the presence of a hemorrhagic component could lead to the diagnosis of endometriosis, this finding is not specific and is common to other pathologies (malignant lesions). It is useful to consider the coexistence of pelvic/abdominal endometriotic lesions, the correlation of symptoms with the menstrual cycle or, on the contrary, a history of previous pancreatitis.

Differential diagnosis includes cystic malignancies, pseudocysts, and pseudopapillary solid tumors of the pancreas. Mucinous pancreatic cysts can be premalignant, contain a characteristic ovarian-like stroma in their inner lining and have no communication with the pancreatic duct, and

Table 4. Patient characteristics, presentation, and treatment of included case reports of hepatic endometriosis.

Author Year	Patients No. (age)	Main signs and symptoms	Pelvic/abdominal endometriosis	Pathogenetic hypothesis	Therapy	Follow-up (months/years)
Eychenn C <i>et al.</i> 2019 [133]	1 (67)	Postmenopausal Voluminous cyst casual discovered	NO		Surgical biopsy + Letrozole	1 year
Liu K <i>et al.</i> 2015 [136]	1 (36)	RUQ pain. 6.5 × 6 cm cystic mass	NO	Lymphovascular Spread	Liver resection	3 months
Keramidas D <i>et al.</i> 2018 [137]	1 (40)	Asymptomatic, large cystic mass of left hepatic lobe		Transcoelomic spread and implantation	LPS cystectomy	NR
Roesch-Dietlen F <i>et al.</i> 2011 [138]	1 (25)	RUQ tenderness Right lobe hemorrhagic mass (6 × 5 cm)	Parietal peritoneum		LPS biopsy + danazol	NR
Nezhat c. <i>Et al.</i> 2005 [139]	2 (36, 30)	1: epigastric pain, 3 cm cyst right lobe 2: chronic pelvic pain. 2.7 cm solid mass right lobe	1: pelvic extensive 2: pelvic extensive	Combination of implantation, coelomic metaplasia and lymphovascular spread	LPS excision	NR
Reid GD <i>et al.</i> 2003 [140]	1 (46)	RUQ catamenial pain, 10 cm lesion of right lobe	Pelvic severe	Primary diaphragmatic disease	LPT right hepatectomy	1 year
Asran M <i>et al.</i> 2010 [141]	1 (61)	Epigastric pain	Pelvic and intestinal	Blood/lymphatic dissemination	Percutaneous true-cut biopsy	
Sherif A M <i>et al.</i> 2016 [142]	1 (44)	RUQ pain, 3 cm hypodense subcapsular lesion right	Severe pelvic	Implantation/coelomic metaplasia	LPT Hepatic segmentectomy	2 years
Rivkine E <i>et al.</i> 2012 [143]	1 (51)	Epigastric pain, 8 × 7.5 necrotic tumor left	NO	Venous/lymphatic dissemination	Left lobectomy with diaphragmatic resection	6 months
Fluegen G <i>et al.</i> 2013 [144]	1 (32)	RQU persistent pain, Right 9.5 × 12 cm central liver cyst	NO	Implantation theory	LPT excision	NR
Goldsmith PJ <i>et al.</i> 2009 [145]	1 (48)	Upper quadrant pain, Cystic mass left liver	Severe pelvic	Trans coelomic spread	LPT non anatomical resection	7 years
Rana P <i>Et al.</i> 2019 [146]	1 (42)	RQU episodic severe pain, 4 × 1.8 multi septated cyst in the left lobe	NO	Lymphatic spread	LPT left hepatic resection	2 months
De Riggi MA <i>et al.</i> 2016 [147]	1 (27)	LUQ tenderness, 30 cm hepatic cyst left lobe	NO	Lymphovascular spread	LPT tailored resection	NR
Huang WT <i>et al.</i> 2002 [148]	1 (56)	Intermittent epigastric pain, 9 × 6 cm mass left lobe	Severe pelvic	Lymphatic/blood spread	Lpt left hepatic lobectomy	NR
Cantos Pallares M <i>et al.</i> 2011 [149]	1 (46)	RUQ pain, 4.8 cm cyst right lobe	NO	Dissemination and implantation of endometrial cells	LPS resection with harmonic scalpel	NR

RUQ, Right Upper Quadrant; LPT, Laparotomy; LPS, Laparoscopy.

Table 5. Patients characteristics, presentation and treatment of included case reports with Pancreatic endometriosis.

Author (year)	Patient' no (age)	Main symptoms, signs	Concomitant endometriosis	Pathogenetic hypotesis	Therapy	Follow-up
Karaosmanoglu AI, <i>et al.</i> (2020) [154]	1 (38)	Epigastric pain, cyst 9 × 8.5 cm	NO		Distal pancreatectomy	NR
Yamamoto R, <i>et al.</i> (2019) [157]	1 (26)	Left abdominal pain, 12 cm cyst	NO	NR	Distal pancreatectomy	NR
Plodeck V, <i>et al.</i> (2016) [156]	1 (68)	Left abdominal pain, partly cystic, partly solid lesion 3 × 2.5 cm	NO	Coelomic metaplasia, embryonic mullerian rests	Left pancreatectomy	5 years
Tunugunta A, <i>et al.</i> (2004) [158]	1 (34)	Severe abdominal pain, 8 × 8 cm cystic mass in the tail	NO	Menstrual endometrial implantation/coelomic metaplasia	LPT distal pancreatectomy	NR
Soo Lee D, <i>et al.</i> (2002) [159]	1 (21)	Epigastric pain+ weight loss, 3.5 × 4 cm cystic mass of the body	NO	Coelomic metaplasia/lymphatic and vascular dissemination	LPT partial pancreatectomy	NR
Piccinni G, <i>et al.</i> (2016) [160]	1 (26)	Postpartum abdominal pain, 7.5 × 5.5 cm cystic mesenteric mass	NO	NR	LPS excision	NR
Assifi MM, <i>et al.</i> (2014) [153]	2 (63.32)	1: asymptomatic, tail cyst 2: epigastric pain, body cyst	NR	NR	Distal pancreatectomy in both cases	NR
Verbeke C, <i>et al.</i> (1996) [161]	1 (28)	Abdominal pain, 10 × 4.5 cm cyst, body	NO	NR	Distal pancreatectomy	NR
Loja Oropeza D <i>et al.</i> (2009) [162]	1 (23)	Epigastric pain, 10 × 10 cm cyst tail	NO	Retrograde menstruation	Distal pancreatectomy	NR
Oishi M, <i>et al.</i> (2011) [152]	1 (35)	Severe recurrent epigastralgia, 3 × 2.5 cm body cyst	NO	Coelomic metaplasia	Distal pancreatectomy	NR

NR, Not Reported.

are typically located on the body and tail, appearing solitary. On the contrary, IPMN pseudocysts are in communication with the branches of the pancreatic duct, affecting women between 40 and 50 years of age. They appear as complex masses, partly solid, partly cystic, affect women of childbearing age and are often characterized by arterial enhancing and calcifications [157]. When the imaging findings are not specific (as in most cases), surgical findings are indicated; on histological examination, pancreatic endometriotic lesions always reveal the presence of endometrial glands and stroma, associated with hemorrhages and macrophages filled with hemosiderin [158].

For patients of childbearing age with recurrent abdominal pain and findings of pancreatic cystic lesions, and where malignancy is not evident, it is advisable to institute ovarian suppression therapy, at least initially. If therapy is effective, surgery becomes a second priority and continuation of hormone therapy is indicated. If, on the other hand, ovarian suppression therapy does not produce benefits, surgical excisional therapy of the lesions found is a priority (Table 5, Ref. [152,154–162]).

9. Conclusions

Extrapelvic endometriosis, especially in its rare forms, presents with a great variety of signs and symptoms. The frequent catamenial recurrence of clinical manifestations is of great help in the diagnosis, especially when it comes to women of reproductive age. Unfortunately, delays in diagnosis are common and can only be avoided with a high index of clinical suspicion. Surgical excisional therapy is often the best solution for definitive therapy, but sometimes medical therapy is also useful, together with a multidisciplinary approach. The chances of healing are closely linked to early diagnosis which avoids the aggravation of anatomical lesions.

Author contributions

FF and SDF are responsible for idea and data collection. AnB and SS contributed to manuscript preparation. AlB and MC analyzed the data and coordinated efforts. All named Authors approved final version.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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