Combination therapy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent leiomyomatosis peritonealis disseminata with endometriosis: a case report

Xiaoli Xiao  
Aerospace Center Hospital

Cong Wang  
Aerospace Center Hospital

Yuyuan Zhang  
Aerospace Center Hospital

Fang Li  
Aerospace Center Hospital

Huan Zhang  
Aerospace Center Hospital

Ruiqing Ma (✉ maruiqing2014@126.com)  
Aerospace Center Hospital

Xichao Zhai  
Aerospace Center Hospital

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Case Report

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Abstract

Background

Leiomyomatosis peritonealis disseminata (LPD) is a non-metastatic, homologous, multicentric benign disorder characterized by small leiomyomas scattered over the peritoneum and omentum. It is a rare and benign disease with invasive potential. LPD mainly attacks women of childbearing age, but it has also been reported in postmenopausal women, men, and young children. Non-specific clinical and imaging findings of LPD lead to difficult diagnoses and treatment.

Case presentation

This study reports the case of a patient with recurrent LPD with endometriosis after multiple myomectomies and hysterectomy, who presented recurrent abdominal pain with progressive exacerbation. Imaging examinations showed irregular shadows in the pelvic cavity and multiple nodular changes in the peritoneum, which were considered malignant lesions. A solid mass sized 10 mm × 9 mm × 10 mm in the inferior pelvis and nodules scattered over the surface of pelvic and abdominal organs and the peritoneum were detected during the surgery. The patient was treated with cytoreductive surgery (CRS), peritonectomy, ovarian ablation, and hyperthermic intraperitoneal chemotherapy (HIPEC). The surgery was challenging, and the intraoperative bleeding reached 900 ml. However, the patient recovered well and achieved a tumor-free survival of 13 months.

Conclusions

It was concluded that a combination of CRS, peritonectomy, ovarian ablation, and HIPEC is an effective therapeutic strategy for recurrent LPD.

Background

Leiomyomatosis peritonealis disseminata (LPD) was initially reported in 1952 [1] as a non-metastatic, homologous, multicentric benign disorder characterized by small leiomyomas scattered over the peritoneum and omentum. It is a benign disease with great invasive potential. LPD mainly affects women of childbearing age. Most LPD cases are asymptomatic and are occasionally diagnosed during surgery. In some cases, abdominal pain and distention may be present. Currently, the pathogenesis of LPD has not been fully elucidated, which is closely linked with hormone dependence, the metaplastic potential of stem cells within the peritoneal cavity, and iatrogenic responses. Surgery is the main treatment of LPD, and the surgical scope should be individualized according to fertility requirements. This case report describes a woman of childbearing age with recurrent LPD after multiple surgeries and endometriosis. After cytoreductive surgery (CRS), peritonectomy, ovarian ablation, and hyperthermic intraperitoneal chemotherapy (HIPEC), the patient achieved a tumor-free survival of 13 months.
Case Presentation

A 40-year-old woman, G4P1, was admitted on October 11, 2021, due to pain in the right lower abdomen for eight years and an aggravation with a sense of abdominal expanding for one month. The patient underwent a cesarean section in 2009 (A hospital) and a laparoscopic myomectomy in 2012 in the same hospital due to a single uterine fibroid (5 cm). The patient had been suffering from pain in the right lower abdomen without an obvious inducement since 2013. In 2015 and 2018, she underwent the removal of multiple uterine fibroids with laparotomy and cyst removal in the bilateral ovarian endometriomas (B and C hospitals). Gonadotropin-releasing hormone agonist (GnRH-a) therapy was postoperatively performed for six cycles. In November 2018, the patient underwent hysteroscopic placement of the levonorgestrel-releasing intrauterine system (D hospital). Ultrasound-guided puncture of the endometriomas was performed in 2019 (D hospital). In 2020, the patient was surgically treated with a total abdominal hysterectomy, adnexectomy on the right side, salpingectomy on the left side, cyst removal of the ovarian endometrioma on the left side, and lysis of intestinal adhesions (D hospital). Postoperative pathological examinations showed a nodule in the pelvic cavity (highly suspected of lipoleiomyoma), leiomyoma, adenomyoma in the uterus and cervix, endometriosis on the right-side accessory, and an endometrioma on the left ovary. After three cycles of postoperative GnRH-a therapy, a re-examination of ultrasound at the two-month follow-up showed a solid mass sized 4 cm. The pain in the right lower abdomen, however, was not relieved after the surgery. It increased progressively until requiring oral painkillers for relief. A pelvic magnetic resonance imaging (MRI) scan and contrast-enhanced MRI performed on August 6, 2021, showed a larger pelvic lesion occupying the anterior rectum than before (9.3 mm × 8.6 mm × 8.6 mm), and multiple nodules in the peritoneum and mesentery were suspected to be malignant (E hospital). A biopsy of the pelvic cystic lesion on August 18, 2021, suggested a smooth muscle tumor, with inadequate evidence for malignancy (F hospital) (Fig. 1). The patient refused to be orally medicated with highly effective progestogen due to the fear of thrombosis. The patient asked for medical help in Aerospace Center Hospital due to one-month pain aggravation in the right lower abdomen, heavy feeling, and occasional lumbago for one to seven hours, which could be relieved through the oral administration of tramadol. The patient had a smoking history of two years, with seven cigarettes per day, and she had stopped smoking five years ago.

Physical examinations showed a painful appearance and forced posture. The abdomen was soft, with tenderness in the lower part. Rebound tenderness was negative. The pelvic examination showed no hymen and obstruction in the vagina, and its formerly sutured end remained smooth. A mass sized 10 cm was palpated in the pelvic cavity and fixed in the anterior rectum with a clear boundary, hard texture, obvious tenderness, and poor mobility. The rectal mucosa was smooth. A hard mass was palpated in the anterior rectum at 7 cm away from the anus, showing good mobility, no tenderness, and no bleeding in the digital rectal examination.

Pelvic MRI and computed tomography (CT) showed an irregular mass in the pelvic cavity and multiple nodular changes on the peritoneum, which were considered malignant (Fig. 2A-G). During the surgery, a solid mass in the inferior pelvis sized 10 mm × 9 mm × 10 mm was found. Multiple nodules were
scattered over the surface of the pelvic and abdominal organs and the peritoneum (Fig. 3A-D). The cancer antigen 125 (CA125) level was 35.08 U/ml.

The exploratory laparotomy was performed in Aerospace Center Hospital on October 18, 2021. Free ascites was undetectable. Miliary nodules were seen in the peritoneum below the original incision. Scattered miliary nodules sized 0.2–0.5 cm were seen in the peritoneum of the right iliac fossa, greater omentum, jejunum, and mesoappendix. Densely scattered nodules sized 0.5–1.5 cm were seen in the descending colon, epiploic appendices of the sigmoid colon, and mesosigmoid. The pelvic cavity was sealed with neoplastic adhesions. Peritoneum and epiploic appendices of the sigmoid colon were intraoperatively collected and subjected to a frozen section pathology, suggesting the spindle cell tumor of the recurrent LPD (malignancy could not be excluded). The patient was then treated with CRS to resect the pelvic peritoneum, vaginal stump, serous membrane of the sigmoid colon, mesorectum with tumor implantation, left ovary, pelvic tumor, greater omentum, and appendix. Nodules on the mesangial and serous membrane surfaces of the small intestine were completely removed by argon plasma coagulation or the surgical resection of the serous membrane, achieving a completeness of cytoreduction (CC) score of 0 (Fig. 3E, F).

The patient had widely implanted abdominal nodules, and the intraoperative frozen section pathology could not exclude malignancy. After communication with family members, a 60-min HIPEC treatment consisting of 80 mg cisplatin in 4000 ml of normal saline was performed with the water inlet and outlet temperatures of 43.5°C and 42°C, respectively. Surgical procedures were extremely challenging and lasted for seven hours. Intraoperative blood loss amounted to 900 ml, and transfusion therapy was not given. The patient was postoperatively transferred to the intensive care unit. Postoperative pathology suggested: (1) multiple spindle cell tumors in the abdominal wall, epiploic appendices of the sigmoid colon, mesosigmoid, pelvic cavity, greater omentum, ascending mesocolon, peritoneum of the right iliac fossa, and mesoappendix, which were considered LPD lesions, with sizes ranging from 0.5 cm × 0.5 cm × 0.5 cm to 10 cm × 8 cm × 8 cm; (2) pelvic tumor from endometriosis; (3) corpus luteum and corpus albicans in the left ovary; (4) chronic appendicitis with acute inflammatory exudates in the mesentery and serosa of the appendix; (5) fibrofatty tissues in the ligamentum teres hepatitis, and tumors were not detectable. Immunohistochemistry data revealed CD34 in the blood vessels (+), CD117 (-), S-100 (-), smooth muscle markers (SMA) (+), desmin (+), Dog-1 (-), CD10 (focal positive), ER (+), PR (+), and Ki-67 (+, 2%) (Fig. 4A-I). The patient was discharged at 11 days postoperatively, followed up for 13 months, and found to have achieved tumor-free survival (Fig. 2H-I). Furthermore, the abdominal pain was completely relieved. However, the patient gradually presented with menopausal symptoms, such as hot flashes and pelvic pain. Hormone testing results were as follows: luteinizing hormone, 44.87 IU/L; follicle-stimulating hormone, 108.8 IU/L; prolactin (PRL), 6.62 µg/L; progesterone (P), 0.1 6ng/mL; estradiol (E2), < 15 pg/ml; and testosterone (T), 12.08 ng/dL. The CA125 level dropped to 4.0 U/ml.

**Discussion And Conclusions**
Leiomyomatosis peritonealis disseminata was initially reported in 1952 [1]. It is a non-metastatic, homologous, multicentric benign disorder characterized by small leiomyomas scattered over the peritoneum and omentum. LPD with a lesion size of over 15 cm has also been reported [2]. It is a rare disease with invasive potential, but it is histologically benign. LPD mainly affects women of childbearing age, but it occasionally affects postmenopausal women [3, 4], young children, and men [5]. Most LPD cases are asymptomatic and non-specific. As a result, the exact prevalence of LPD is unclear [6].

The pathogenesis of LPD has not been fully elucidated. The following theories are considered to be closely linked with LPD. First, the initially proposed hormone dependence theory. LPD is a hormone-dependent tumor detected in pregnant women and those who received long-term oral estrogen and progesterone, had estrogen-secreting adrenal tumors, or underwent ovarian stimulation. LPD lesions shrank or regressed after GnRH-a therapy or treatment with aromatase inhibitors, further confirming the hormone dependence theory. Moreover, positive expressions of estrogen and progesterone receptors in LPD lesions support this theory. In this case, postoperative positive estrogen and progesterone receptors and 13 months of tumor-free survival after ovarian ablation were consistent with the hormone dependence theory. However, short-term ovarian ablation with six cycles of GnRH-a after the fourth operation and three cycles of GnRH-a after the seventh unilateral oophorectomy failed to prevent the development of uterine fibroids, adenomyoma, and endometriosis. It could also not prevent the recurrence of LPD, which could not be explained by the hormone dependence theory. LPD also affects postmenopausal women, men, and infants, indicating the potential involvement of other theories.

Second, LPD may be caused by the metaplastic potential of stem cells within the peritoneal cavity [7]. Estrogen stimulates peritoneal mesenchymal stem cells to proliferate and differentiate into myocytes, myofibroblasts, and fibroblasts. The patient had recurrent uterine fibroids and adenomyoma, endometriosis, and massive endometrial glands and stroma in the smooth muscle bundle of the largest tumor in the inferior pelvis with cavities and bleeding. The above evidence indicates that the recurrent LPD, uterine fibroids, and endometriosis may originate from totipotent stem cells in the subcutaneous peritoneum, which is consistent with a previous case report involving seven LPD patients with endometriosis within the same lesions [8].

Third, the iatrogenic theory is involved in the pathogenesis of LPD. Most of the reported LPD cases have a medical history of laparoscopic myomectomy, especially in the early development of laparoscopy [9]. An unprotected intraabdominal morcellation of uterine tissues after resecting uterine fibroids has been widely performed, which, however, has been gradually limited by the development of parasitic myomas. During the rotatory resection of uterine fibroids, small pieces and spray-like fibroid tissues and cells undetected by the naked eye remain in the peritoneum or omentum and eventually develop into LPD with a dependence on angiogenesis. Such a process may last years or even decades [10, 11]. Miyaka et al. [12] reported a case of LPD and confirmed the monoclonal origin of uterine leiomyomas in the first surgery and LPD tumors in the second and third surgeries using the nonrandom X-chromosome inactivation pattern. The patient was treated with an unindicated cesarean section followed by a laparoscopic myomectomy. According to the operation time and the hospital, unprotected intraabdominal morcellation
was not applied. Immunohistochemical staining showed that SMA and desmin were strongly positive, suggesting that LPD shares partial common molecular and cytogenetic characteristics with those of uterine leiomyoma. It cannot be ruled out that the two surgeries jointly contributed to the occurrence of LPD and endometriosis, which accelerate the generation of totipotent stem cells in the subcutaneous peritoneum.

Fourth, genetics theory is linked with the pathogenesis of LPD, and familial clustering of LPD has been reported [6]. Chromosomal abnormalities [12] or mutations in the MED12 gene [13] are involved in the pathogenesis of LPD. This study performed karyotype analysis, and the data showed a 46, XX karyotype (Fig. 5). A history of uterine fibroids has not been reported within three generations for the patient. Whether smoking-induced gene mutations are the cause of LPD in this case, remains unknown. Unfortunately, the patient refused to be examined by genetic testing due to the high medical cost. It is believed that the cause of LPD in this case could not be explained by a single theory due to rapid development, the short onset, and the progressive aggravation.

It is difficult to distinguish LPD from peritoneal implants of small malignancies based on preoperative imaging. Moreover, clinical manifestations of LPD are atypical and are mainly diagnosed through postoperative pathology. So far, global consensuses for the treatment of LPD are scant [14]. Local high-level amplifications of the CDK4, MYC, NBN, and DAXX genes have been detected in LPD cases by next-generation sequencing, with at least a four-fold increase in copy numbers. In addition, their immunohistochemical stainings in leiomyoma, LPD, and leiomyosarcoma demonstrate that the expression profile of LPD is more similar to that of leiomyosarcoma [10, 15]. Considering the high rate of malignancy, surgery is preferred for patients with LPD. A debulking surgery that removes all macroscopic LPD lesions as much as possible, combined with organ resection, is the conventional option for patients with LPD without fertility requirements [9, 16]. In this case report, GnRH-a therapy was immediately given to the patient after total abdominal hysterectomy, adnexectomy on the right side, and resection of LPD lesions in the intestinal tube. However, LPD and endometrioma recurred in a short period, which may be attributed to the unresected peritoneum and omentum and the differentiation of the totipotent stem cells in the subcutaneous peritoneum into smooth muscle cells, endometrial glands, and mesenchyme.

At present, CRS achieved by peritonectomy procedures and en-bloc resection of the viscera has been widely applied to treat tumors on the surface of the peritoneum, which significantly reduces the recurrent rate and enhances long-term survival. Multiple miliary nodules were examined in the patient’s pelvic cavity, peritoneum, and omentum. The assessment of tumor burdens during surgical exploration is of great significance and ensures the feasibility of peritonectomy [17].

CRS is the most effective treatment for advanced epithelial ovarian malignancies, followed by intravenous paclitaxel and platinum chemotherapy. Systemic intravenous chemotherapy, however, is less effective in the treatment of metastases due to poor peritoneal blood flow and less penetration of drugs into tumors. HIPEC has become a novel alternative that applies heated chemotherapy directly to abdominal tumors, causing cytotoxicity. HIPEC has emerged as an alternative to adjuvant or neoadjuvant
therapy for advanced ovarian cancer due to the high local exposure and low concentrations in the circulation [18]. Abdominal tumors with poor vascularization can also benefit from HIPEC. In addition, the peritoneal plasma barrier limits the absorption of high-dose chemotherapeutic drugs into the blood, minimizing systemic toxicity and maximizing local effects. During the surgery, malignant peritoneal implantation and metastasis could not be determined by the intraoperative frozen section pathology. After full communication with family members, HIPEC was actively performed to clear residual small tumors and free tumor cells in the pelvic cavity as much as possible, even though her CC score was 0. Heat is directly cytotoxic and enhances the penetration of chemotherapeutic drugs into tumors and synergizes with cisplatin to induce apoptosis in residual leiomyoma cells, which minimizes systemic adverse events. The patient did not have HIPEC-induced adverse events, and the postoperative liver and kidney functions were normal. The therapeutic effect of HIPEC in benign-disseminated tumors needs further exploration.

**Conclusion**

The study indicated the efficacy of CRS and ovarian ablation in recurrent LPD combined with endometriosis. This study reported, for the first time, the application of HIPEC to a patient with undetermined intraoperative pathology and extensive involvement of tumors in the abdominal cavity. This treatment may serve as a novel therapeutic strategy for recurrent LPD combined with endometriosis. The patient’s quality of life after ovarian ablation deserves attention. Perimenopausal symptoms and osteoporosis caused by low-level estrogen are the main adverse events after ovarian ablation in women of childbearing age. Moreover, low-level estrogen poses a long-term influence on bone metabolism, and the patient developed obvious pelvic pain after the surgery. Based on the add-back therapy for endometriosis after GnRH-a administration, the effect of low-dose estrogen supplements that improve the quality of life will be closely monitored [19]. In addition, considering the iatrogenic theory, the morcellation of uterine fibroids should be carried out with caution to avoid fragments remaining and prevent the development of LPD [20].

**List Of Abbreviations**

Leiomyomatosis peritonealis disseminata (LPD)

After cytoreductive surgery (CRS)

hyperthermic intraperitoneal chemotherapy (HIPEC)

Gonadotropin-releasing hormone agonist (GnRH-a)

magnetic resonance imaging (MRI)

computed tomography (CT)
cancer antigen 125 (CA125)

completeness of cytoreduction (CC)

Declarations

**Ethics approval and consent to participate:** The study was reviewed and approved by the Ethics Committees of the Aerospace Center Hospital. Written consent was obtained from the patient.

**Consent for publication:** Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal.

**Availability of data and materials:** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

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**Authors' contributions:** XX, YZ, YL, and HZ provided study material or patients; XX and CW contributed to the draft of the manuscript; RM and XZ revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript to be submitted. All authors agreed to be accountable for all aspects of the work; ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**References**


Figures

**Figure 1**

Timeline for the treatment
Figure 2

A-D. MRI scans showed multiple shadows of soft tissues (white arrow) with uneven signals and confluent intensity on T1WI (hypointensity, A), T2WI (mixed hyperintensity, B), DWI (hyperintensity, C), and ADC (hypointensity, D). The signal was uneven in the lesion, and multiple hyperintense lesions on T1WI and mixed hypointense lesions on T2WI were seen (red arrow). The lesion had a blurred margin with the adjacent rectum and sigmoid colon. E-G. Plain computed tomography (CT) (E), the CT arterial phase (F), and the venous phase (G) showed irregular lobular mass shadows behind the bladder (white arrow), in which the intensity was uneven and cystic regions were detectable (red arrow). The contrast-enhanced CT showed inhomogeneous enhancement in the lesion with local ring enhancement. Enhancement was not detectable in the cystic regions. The rectum and sigmoid colon were partially surrounded, and the boundary with the posterior wall of the bladder was blurred. Postoperative CT review: there was no abnormal density shadow in the pelvic cavity (H-I).
Figure 3

A-C. Surgical explorations of diffuse nodule implantations of the greater omentum (A), pelvic masses (B), and nodule implantations in the small intestinal mesentery (C). D. Isolation of mesentery and serosa of the small intestine. E. Postoperative pelvic cavity. F. Postoperative small intestinal mesentery.

Figure 4
Pathological changes of the patient. A. H&E staining of multiple leiomyomas in the peritoneum of the right iliac fossa, with a clear boundary (magnification = 10×). B. H&E staining of braided spindle cells and scattered small muscular vessels, and cellular atypia and necrosis were not detectable (magnification = 100×). C. H&E staining of acidophilic spindle tumor cells with a blunt nucleus and enriched cytoplasm (magnification = 400×). D. H&E staining showed typical morphological characteristics of leiomyomas in the mesosigmoid and scattered thick and thin blood vessels (magnification = 100×). E. H&E staining showed cystic dilation and hemorrhage in the leiomyoma (magnification = 20×). F. H&E staining showed endometrial glands and stroma and hemosiderin deposition in the partial stroma (magnification = 100×). G, H, Immunohistochemical staining of smooth muscle markers (G) and desmin (I). Magnification = 200×. I. Immunohistochemical staining of Ki-67, showing the Ki-67 index of 2% (magnification = 100×).

**Figure 5**

CEPX/CEPY FISH analysis; red and green spots indicated chromosomes Y and X, respectively, which revealed 100% XX signals (nuc ish (CEPX×2) [500]).