Successful pregnancy after complete resection of leiomyomatosis peritonealis disseminate without recurrence: A case report with next generation sequencing analysis and literature review

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Case report

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Abstract

Background: Peritoneal leiomyomatosis disseminate (LPD) is a rare disease characterized by widespread dissemination of leiomyomas nodules throughout the peritoneal and omental surfaces. Reports of pregnancy with LPD are even rarer. Therefore, there is no clear consensus on the treatment of LPD on pregnancy, and the pathogenesis is still unclear.

Case presentation We reported a case of LPD patient who developed during pregnancy. The patient underwent cesarean section at 32 weeks of gestation while removing all visible tumors, and no LPD lesions were seen in the subsequently cesarean section at full-term. NGS of LPD lesions detected 4 mutations with focal high-level amplifications of CDK4 (Cyclin-dependent kinases 4), NBN (Nibrin), DAXX (Death domain associated protein) and MYC (Myelocytomatosis oncogene). Immunohistochemistry staining analysis among benign leiomyoma, LPD and leiomyosarcoma verified that LPD was an unusual intermediate between benign and malignant uterine smooth muscle tumors. Besides, LPD is a hormonal-dependent leiomyoma. After detailed literature search, we summarized the detailed clinical features and follow-up information of patients with LPD during pregnancy.

Conclusions: This is the first reported LPD case of successful term pregnancy without recurrence, following resection of all visible lesions in prior pregnancy. LPD is an unusual intermediate between benign and malignant uterine smooth muscle tumors.

1. Introduction

Uterine smooth muscle tumors include a variety of tumors, such as benign uterine leiomyoma, malignant leiomyosarcoma and tumors with unusual growth patterns. Uterine leiomyoma is the most common tumor of the female reproductive system[1]. Benign leiomyoma variants mainly include atypical leiomyoma, plexiform leiomyoma, cellular leiomyoma, smooth muscle tumor of uncertain malignant potential[2]. Leiomyosarcoma is uterine malignancy with an aggressive clinical behavior and poor prognosis. Leiomyosarcoma distinguishes from uterine leiomyoma by the presence of coagulative tumor necrosis, severe cellular atypia, extreme cytogenetic instability and elevated mitotic activity[3]. LPD as well as intravenous leiomyomatosis belongs to a class of tumors resembling uterine leiomyoma at both gross and microscopic levels but presenting in unusual locations with recurrent and malignant tendencies[4].

LPD is a rare benign intra-abdominal leiomyoma characterized by multifocal proliferation of smooth muscle-like cells that are histologically similar to uterine leiomyoma[5, 6]. Up to date, there have been no more than 200 cases published, of which approximately half been reported in child-bearing years and only few cases in postmenopausal women[7-9]. LPD lesions always involve the pelvic, the abdominal peritoneum and the omentum. The patients generally presents with no clinical symptoms, however, abdominal pain or abdominal distension do occasionally occur[10]. Clinical examination usually reveals numerous smooth muscle nodules in pelvic, the abdominal peritoneum and the omentum. Histopathology examination suggests benign uterine smooth muscle tumors, rare mitotic activity, without nuclear atypia[11].

However, there is still no standardized guideline for the diagnosis and treatment of LPD. LPD occurs during pregnancy is even rarer, so the treatment is even more uncertain. After a detailed literature research, we summarized 15 articles that reported detailed characteristics of LPD during pregnancy, with a total of 16 patients[9, 12-25], which was seen in Table 1. Most patients did not achieve complete lesion resection, but LPD lesions were significantly reduced or disappeared after delivery, and no recurrence occurred during follow-up. Among the patients with a history

of LPD with re-pregnancy, only 2 cases have been reported in the literature. In one case[23], LPD was present before pregnancy, and the lesion increased rapidly in a short time after receiving assisted reproductive technology, and radical surgery (hysterectomy and bilateral adnexectomy) was performed at 10+ week gestation. Another patient was diagnosed with LPD during the first trimester to full-term cesarean section, but only biopsy was performed, and LPD recurred during the second trimester[18]. Because of the limited number of patients, we are still very confused about the treatment of LPD during pregnancy, and it is still unknown whether patients with a history of LPD can get pregnant again, which makes it very difficult for clinicians to make decision.

2. Case Presentation

2.1 Case

A 19-year-old woman with 32^{+3} weeks of gestation was referred to our hospital due to oligohydramnios. The patient had a history of myomectomy at age 15. At that time of ultrasound examination, there was a mass of 20.0 cm* 8.7 cm in size in the pelvic cavity. Postoperative pathological findings showed cellular uterine leiomyoma.

On admission, both the patient and the fetus were in good condition. Physical examination revealed huge mass in pelvic cavity. Abdominal and pelvic ultrasound confirmed the presence of multiple masses in pelvic, sized 16.9*11.2*10.1cm, 13.1*5.6*6.2cm, 19.2*17.5*12cm respectively next to the gestation without signs of abortion. The masses were connected into large clumps. Abdominal MRI was done to show multiple nodules in the abdominal cavity (Figure 1).

In order to ascertain the diagnosis, an exploratory laparotomy was performed because of aggravated abdominal pain. After delivery the fetus by lower-segment cesarean section, the gynecological oncologist performed further operation. The patient was found to have multiple sporadic leiomyoma in anterior wall of uterus, an 8*6cm leiomyoma in posterior wall of uterus, a 20*15 cm tumor mass in the left pelvis, multiple tumor masses in the right pelvic sized 8*7cm, 7*7cm and 7*5cm separately, up to 10 tumor masses sized 3*2cm in omentum and mesocolon transversum (Figure2 A-D). All macroscopic tumor masses were dissected and removed via an extremely difficult surgery without hysterectomy and bilateral salpingo-oophorectomy because of the patient's strong objection and the consideration of young age. Post-operative pathology determined the diagnosis of LPD with red degeneration. The patient recovered well after surgery and was discharged on the ninth day after removal of the abdominal incision suture.

The patient underwent several ultrasound examinations after surgery and no signs of disease recurrence were found without any continuous treatment. The patient was pregnant again 25 months after the surgery. At 7 weeks of gestation, ultrasound examination revealed a fibroid of about 3.7cm*3.7cm in the posterior wall of the uterus, and ultrasound examination during pregnancy indicated that the fibroid was slowly enlarged without any discomfort symptoms. The patient underwent cesarean section again at 39 weeks of gestation. No abnormal lesions were found in the pelvic and abdominal cavity during the operation, and only a uterine fibroid of about 7cm*6cm was found in the posterior wall of the uterus (Figure 2E). Postoperative pathology suggested uterine leiomyoma. The patient was reviewed at 6 months postoperatively and recovered well.

2.2 NGS (next generation sequencing)

We collected 15 of 4μm tissue sections from FFPE samples of LPD and normal tissue adjacent to the lesion for the genetic analyses. QIAamp DNA FFPE Tissue Kit (QIAGEN, Heidelberg, Germany) was used to extract genomic DNA

according to the manufacturer's instructions.

DNA was profiled using a commercial available capture-based targeted sequencing panel (Burning Rock Biotech Ltd, Guangzhou, China), targeting 295 genes which were closely related to the mechanism of cancer and targeted therapy and spanning 1.5MB of Human genomic regions. DNA shearing, end repair and adaptor ligation was performed by the use of Covaris M220 (Covaris, Inc., MA, US). Fragment sizes ranging from 200bp to 400bp were selected using Agencourt AMPure beads (Beckman Coulter, CA, US) followed by hybridization with capture probes baits, hybrid selection with magnetic beads and PCR amplification. Subsequently, Qubit® 3.0 and Agilent 2100 bioanalyzer (Agilent Technologies Inc., CA, US) was performed to assess the quality and size of the fragments. Indexed samples were sequenced on Nextseq500 sequencer (Illumina, Inc., CA, US) with pair-end reads.

Based on the high throughput sequencing, the copy numbers (CNs) of this LPD patient compared with normal population were demonstrated in Figure 3G. There were four somatic cell lines mutations detected in the lesions. The CNs of CDK4, NBN, DAXX and MYC were all amplified for at least 4 times.

2.3 Hematoxylin-eosin (HE) and immunohistochemistry staining

Hematoxylin-eosin (HE) staining slides of this LPD were shown in Figure 3A. Rich blood supply was revealed in LPD in HE staining analysis (Figure 3B).

Immunohistochemistry staining showed that the tumor was strongly positive for smooth muscle markers, SMA and Desmin (Figure 3C, 3D), which suggested that LPD shared partial molecular cytogenetic characteristics with uterine leiomyoma. Immunohistochemistry of hormone receptors, estrogen receptor (ER) and progesterone receptor (PR) were positive (Figure 3E, 3F).

The immunohistochemistry staining analysis of CDK4, MYC, NBN and DAXX in uterine leiomyoma (10 cases), LPD (4 cases) and leiomyosarcoma (10 cases) revealed that the expression profiles of LPD were more similar to leiomyosarcoma. LPD showed CDK4, NBN, DAXX, MYC moderately and strongly positive and uterine leiomyosarcoma displayed strongly positive. However, the four markers in uterine leiomyoma were slightly positive or negative. Therefore, we can infer the conclusion that LPD is an intermediate disease between benign uterine fibroids and malignant leiomyosarcoma.

3. Discussion And Conclusions

In 1952, Willson and Peale described LPD for the first time[6]. LPD characterized with multiple nodules in various sizes in peritoneal cavity, such as uterus, fallopian tubes, intestine, mesentery, omentum and retroperitoneum[6]. The incidence of LPD was unkown due to its rarity. There have been no more than 200 cases reported in the literature up to date.

LPD was difficult to diagnose before surgery. Although it was a benign disease with excellent prognosis, LPD could behave quasi-malignant behavior, such as recur tendency and spread widely in pelvic and abdominal cavity. LPD should be differentiated from peritoneal metastasis of malignancies. Standard histopathological analysis as well as immunochemistry was in need to diagnose LPD accurately. Microscopically, the knots are composed of smooth muscle arranged like leiomyomas. The cells usually show a lack of atypia and higher mitotic variety[9]. In this study, the patient was suspected to have a malignant tumor in pelvic and peritoneal cavity initially. The diagnosis of LPD was confirmed until the histopathology identified. LPD must be distinguished from malignancies to avoid unnecessary aggressive treatment schedules.

LPD predominantly occurs in females of reproductive age, however, the pathogenesis of LPD is poorly understood. Four popular theories on the pathogenesis of LPD have been mentioned earlier. High levels of estrogen and progesterone, such as oral contraceptives, pregnancy, ovarian stimulation, estrogen-producing ovarian tumors and uterine leiomyoma, have been described in most reported cases[5, 9, 17, 26–28]. In this case, high levels of estrogen and progesterone stimulation also played an essential role in the development of LPD. Pregnancy and uterine leiomyoma together exacerbated the increasing levels of estrogen and progesterone. In this LPD, the tumor cells were strongly positive for ER and PR in immunochemistry analysis, supporting the hypothesis that high levels of estrogen and progesterone playing an important role in the pathogenesis of LPD.

LPD shared some molecular cytogenetic characteristics with uterine leiomyoma, such as SMA and Desmin strongly positive in IHC analysis. The histogenesis of LPD is consistent with that of uterine leiomyoma. However, LPD differentiates distinctly from uterine leiomyoma in phenotype. Uterine leiomyoma is obviously benign, whereas LPD has the quasi-malignant behavior. NGS might provide the potential molecular explanation that would explain this difference in phenotype. Compared with common population, CNs of CDK4, MYC, NBN, DAXX were all amplified for at least 4 times in this LPD. Immunochemistry of the four genes among uterine leiomyoma, LPD and uterine leiomyosarcoma was implied. LPD and uterine leiomyosarcoma both were strong positive for the abovementioned four genes, whereas uterine leiomyoma was slightly positive or negative for the four genes. CNs mutations might play an important role in the pathogenesis mechanism of LPD and identify LPD in phenotype from uterine leiomyoma. Further study is in urgent need to delineate the molecular mechanisms underlying the LPD phenotype. In addition, some literatures have confirmed that LPD will be followed by malignant transformation[29–31]. More importantly, based on the above results, we should pay attention to the potential malignancy of LPD during the treatment and follow-up of LPD.

Most importantly, we will discuss the feasibility and safety of pregnancy in patients with LPD. The few cases reported so far do not provide conclusive evidence, and we have no guidelines to follow. After a comprehensive review of the literature, the following conclusions can be drawn: Firstly, assisted reproductive technology is not recommended for patients with LPD, which may lead to the rapid growth of lesions due to the increased estrogen level, leading to serious adverse consequences. Furthermore, complete excision of the lesion if the condition permits may prevent recurrence of the disease in the subsequent pregnancy. Unfortunately, we can only derive these inferences from only a few case reports, and we need more patients to confirm.

In conclusion, we recommend that all visible lesions should be removed as completely as possible during surgery, which may be a very effective treatment plan in addition to radical surgery, and re-pregnancy may be feasible. LPD is an unusual intermediate between benign and malignant uterine smooth muscle tumors.

Declarations

Ethics approval and consent to participate Ethical approval was obtained from Ethics Committee of Shandong University, and written informed consent was obtained from each patient.

Consent for publication Consent for publication of this case was obtained.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

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

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Authors' contributions: BH and JC conducted the experiment and wrote the manuscript. FY, CJ and MY reviewed the literature. WX conducted the IHC analysis. CL was the attending physician of the patient. All authors read and approved the final manuscript.

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Table

Table 1 The summary of LPD cases occurring during pregnancy

Figures

Author	Age	History of hysteromy-omectomy	Gestational weeks	Complications	Operative methods	Surgical investigation	Follow-up
Summa B[9]	29	No	22^{+6}	Abdominal emergency	Explorative laparotomy and partial nodule resection(22^{+6}w) Cesarean section(28^{+6}w)	Nodules up to 7.3cm on omentum minus, appendices epiploicae, the colon, right adnexa and uterus.	Nodules spontaneously subsided, and no recurrence 1 year after operation.
Hardman WJ [12]	33	No	36	Premature rupture of membrane	Cesarean section and omental biopsies	Multiple firm, round, white-togray omental nodules, sized 0.5*08*1.5cm to 1.5*3*3.5cm	No signs of tumor growth during 43 months of follow-up.
Hardman WJ [12]	36	No	38^{+5}	Placenta previa	Cesarean section and omental biopsies	Multiple firm, round, white-togray omental nodules, sized 0.5*08*1.5cm to 1.5*3*3.5cm	No signs of tumor growth during 146 months of follow-up.
Aterman[13]	22	Yes	Full term	Fetal distress	Cesarean section and noodles biopsies	Firm nodules of variable size on omentum, bowel and the capsule of liver.	Nodules were significantly reduced 4 months after surgery.
TANAK[14]	40	Yes	Unknown	IVF-ET twin pregnancy	Cesarean section and nodules biopsies[1st]. Hysterectomy and tuberculectomy[2nd]	Nodules in peritoneal cavity and both inguinal regions[1st] a large tumor within the right broad ligament and numerous nodules in peritoneal cavity[2nd]	Recurrence occurred 8 months after the 1st surgery, and no recurrence 18 months after 2[nd] surgery
PHILIP[15]	32	No	28	Abdominal pain, ascites	Explorative laparotomy and cesarean section	A large cystic mass arised from the lesser curvature of the stomach, and multiple nodules on peritoneal surfaces, 2 to 3 mm in size.	No intra-abdominal masses were shown on CT 9 months after surgery.
Rubin[16]	27	No	Full term	Active phase arrest	Cesarean section and partial nodule resection	Multiple firm, rubbery nodules scattered throughout the pelvic and omentum	Bone metastasis was found 6 months after surgery, and sarcoma was diagnosed.
Dreyer[17]	26	Unknown	Full term	Vulval haematoma	Explorative laparotomy	Numerous small nodules on the uterine serosa, the serosa of the bowel, the	Lost

						omentum and parietal peritoneum	
Lim[18]	22	Unknown	Full term[1st] 35+ [2nd]	Premature rupture of membrane[2nd]	Cesarean section and noodles biopsies[1st and 2nd]	Uterus, lower abdomen and cul-de-sac were studded with nodules ranged from 0.25 to 3cm[1st] Mesentery, omentum and the liver surface were studded with nodules of massive size and numbers[2nd]	Asymptomatic clinical course 8 month after 2[nd] surgery
Pieslor[19]	32	No	Full term	No	Cesarean section	A short omentum replaced by nodules of firm whitish tissue 3-9 mm in diameter, the bladder was covered by numerous 1-mm white nodules.	Unknown
Nogales[2]	34	Unknown	Full term	Prolonged labor	Cesarean section, total hysterectomy and partial nodule resection	Widely scattered white firm nodules on uterine surface, both broad ligaments, cul-de-sac, omentum, bowel, mesentery and peritoneum	Unknown
Parmley[21.]	36	Unknown	Full term	No	Elective tubal ligation	Multiple, small, firm, white nodules noted on the anterior surface of the uterus, small bowel and peritoneum.	No evidence of intra-peritoneal neoplasia 2 years after surgery
Crosland[22]	29	Unknown	8	Severe hypertension	suction curettage and omentectomy	0.2 to 2.5 cm nodulations on all abdominal and pelvic organs and peritoneum	Nodules decreased in size without detailed months provided
Deering[23]	33	LPD	10+	IVF-ET abdominal pain	hysterectomy, bilateral salpingo-oophorectomy, radical pelvic lymph nodes dissection	The nodules grew rapidly after IVF-ET, reaching a maximum of about 17cm, and did not shrink after termination of pregnancy.	9 months without recurrence after surgery
Kouakou[24]	35	No	Full term	Large fetus size	Cesarean section and omental	Multitude nodules	Postoperative consultation 6

					biopsies	ranging from 0.1 to 0.5 cm scattered throughout the pelvic cavity, right broad ligament, bladder-uterine peritoneum and colon.	weeks after surgery was normal.
Hoynck[25]	35	No	Full term	Fetal distress	Cesarean section, multiple biopsies, omentectomy and right salpingectomy	Multiple firm nodules of varying diameter (0.5-4 cm) on the uterus, the right tube ,the peritoneum of intestines and omentum	Nearly complete disappearance 12 weeks after surgery and in good health for the following 3 years

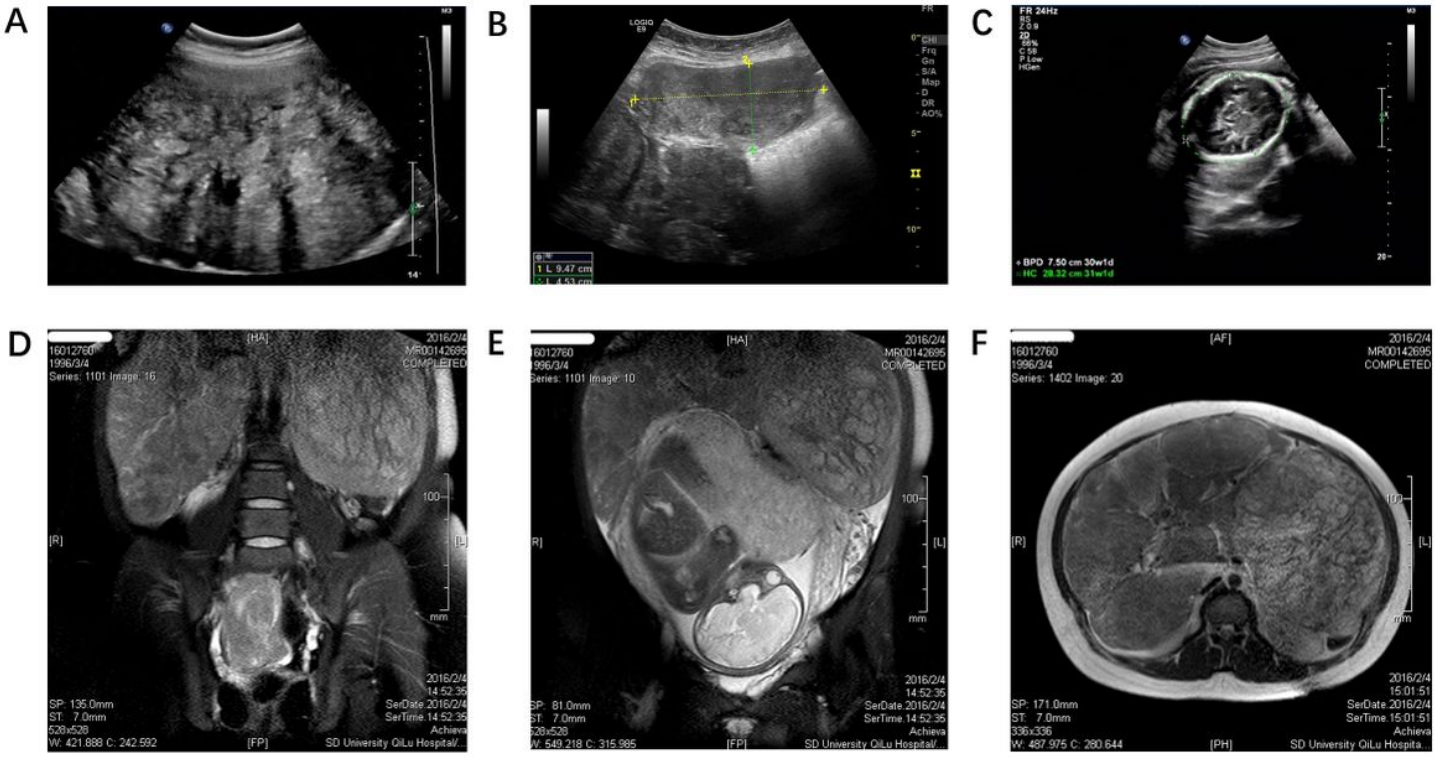

Figure 1

Ultrasound and MRI showed the presence of multiple masses in the pelvis. (A, B) Ultrasound showed huge mass in the pelvis. (C) Fetal head in ultrasound. (D) Multiple huge masses in the pelvis were shown in MRI. (E-F) The fetal was squeezed by huge masses in MRI.

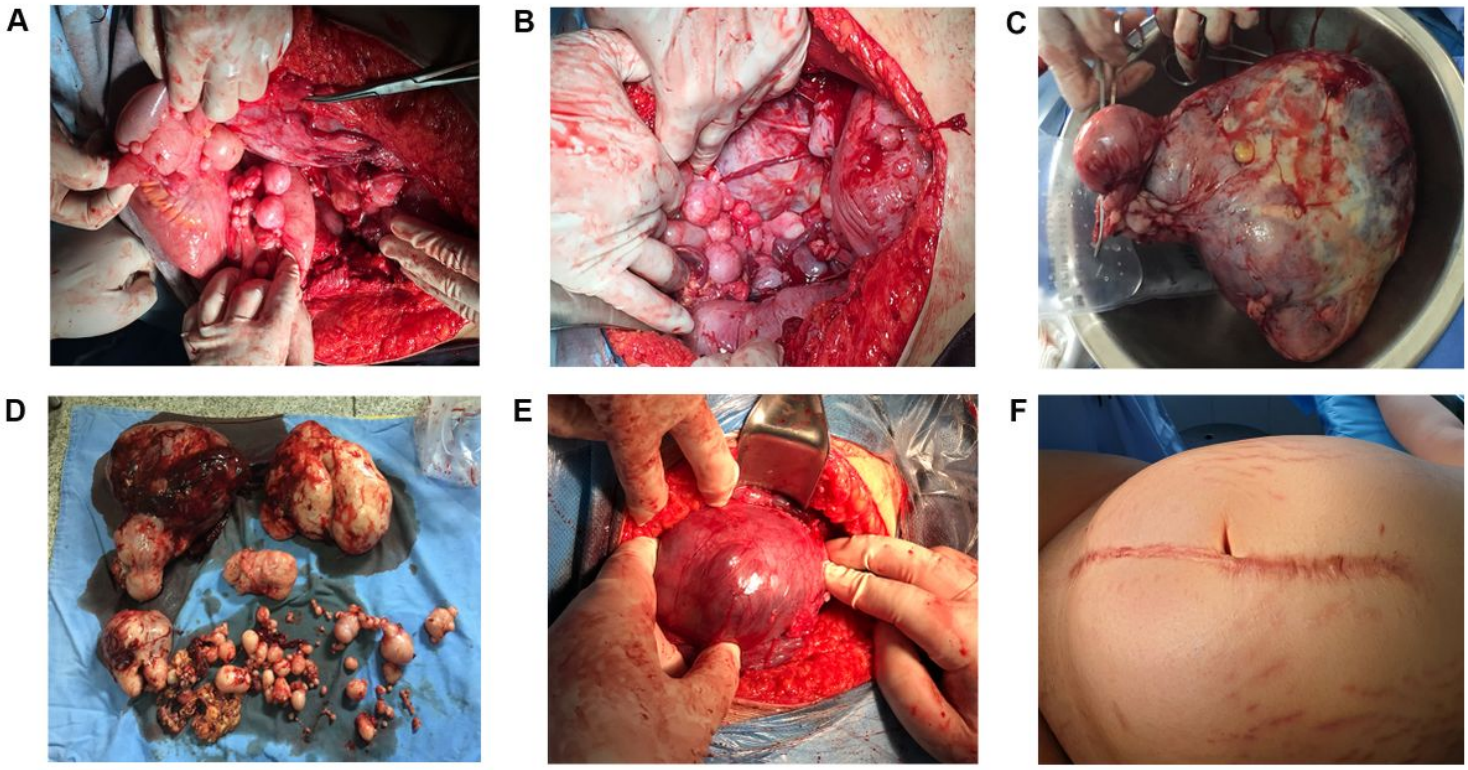

Figure 2

Gross features of LPD during laparotomy. (A-B) Concentrated myoma tubercle like cysts on the surface of the uterine, the intestine and mesentery. (C) The resected huge myoma. (D) All myomas removed in laparotomy, two large myomas, two moderate myomas and multiple small myomas. (E) A single uterine fibroid was found in the posterior wall of the uterus in the second cesarean section. (F) Abdominal scar of the first cesarean section.

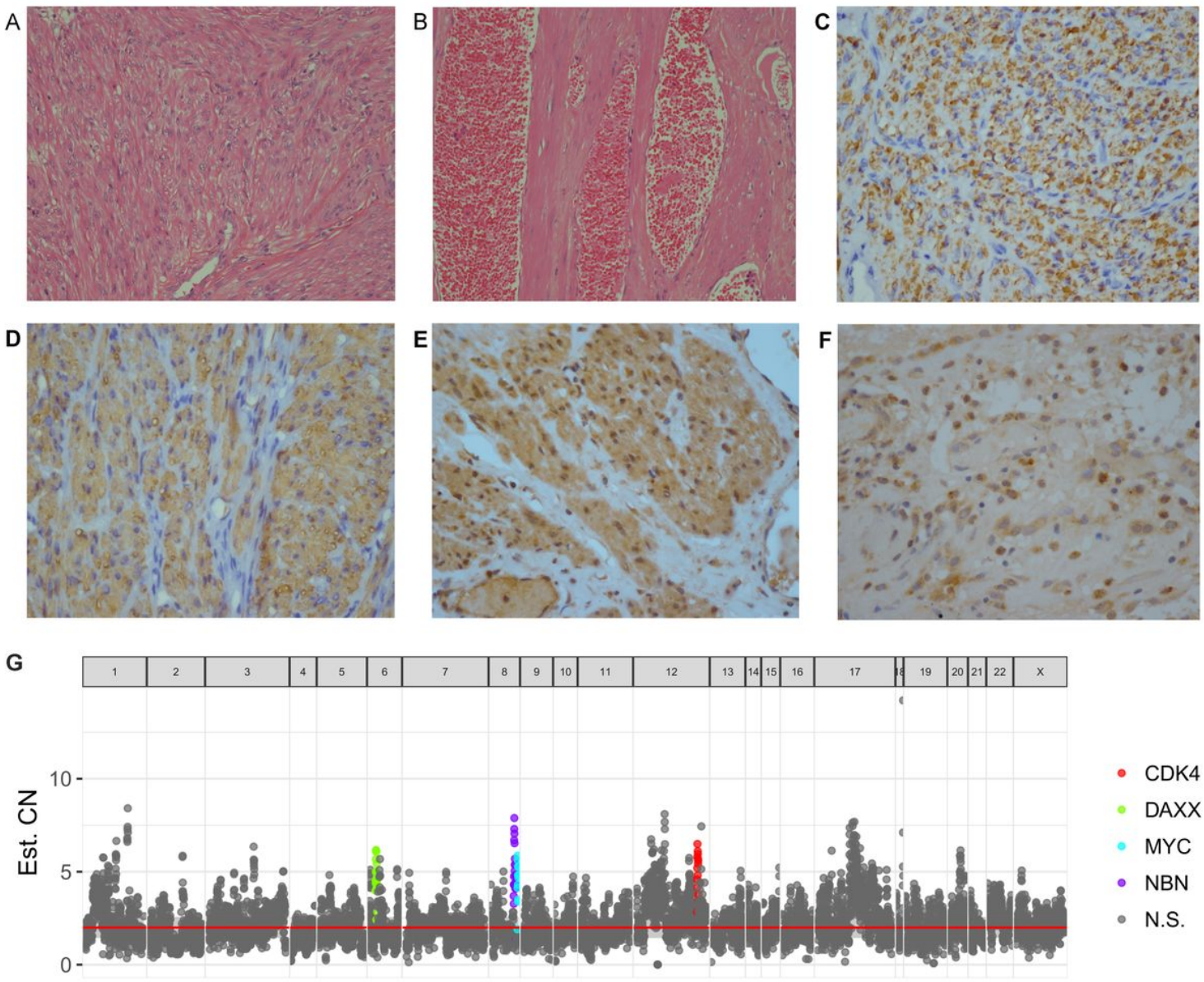

Figure 3

HE staining and immunohistochemistry analysis of LPD. (A-B) HE staining of this LPD, suggesting benign myoma with rich blood supply. (C) Immunohistochemistry staining of Desmin, 40×. (D) Immunohistochemistry staining of SMA, 40×. (E) Immunohistochemistry of estrogen receptor (ER), 40×. ER was strongly positive in LPD. (F) Immunohistochemistry of progesterone receptor (PR), 40×. PR was strongly positive in LPD. (G) Distribution plot of gene copy number in NGS of this LPD. CDK4, DAXX, MYC, NBN were significantly amplified (red = CDK4, green = DAXX, blue = MYC, purple = NBN).

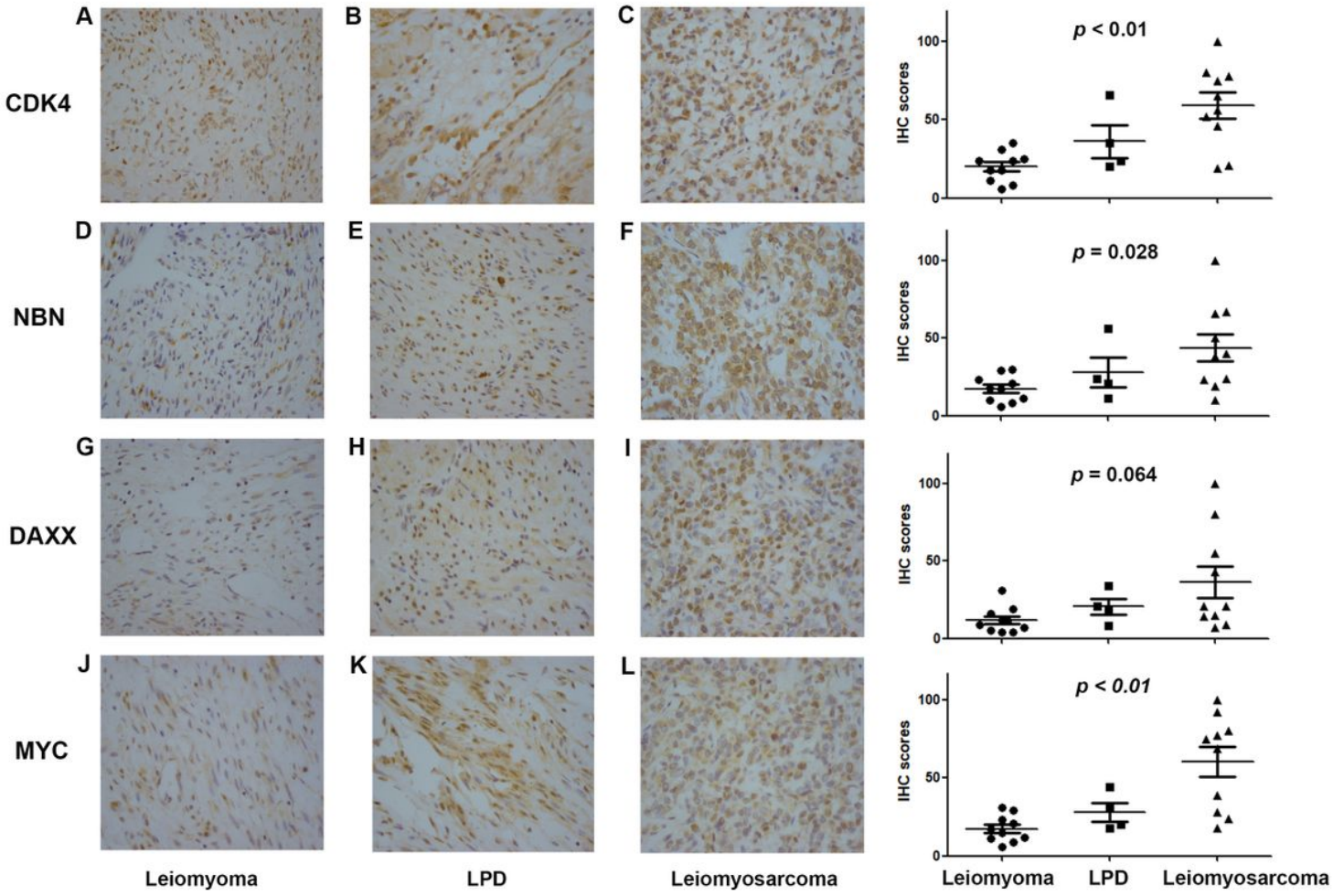

Figure 4

Immunohistochemistry staining analysis of CDK4, NBN, DAXX and MYC in leiomyoma, LPD and leiomyosarcoma, suggesting that LPD is an unusual intermediate between benign and malignant uterine smooth muscle tumors.