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Leiomyomatosis Peritonealis Disseminata Positive for Progesterone Receptor

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None

Patient: Female, 30
Final Diagnosis: Leiomyomatosis
Symptoms: Abnormal finding in abdominal-pelvic CT scan
Medication: —
Clinical Procedure: Surgical tumorectomy
Specialty: Oncology

Objective: Rare disease

Background: Leiomyomatosis peritonealis disseminata (LPD) is a rare condition that occurs in reproductive-age women. The pathogenesis of LPD is considered to be related to female sex hormones.

Case Report: A 30-year-old woman who had undergone an ovariectomy due to calcified thecoma at 24 years of age and had delivered a baby boy at 29 years of age showed abnormal abdominal-pelvic masses in a computed tomography scan. The peritoneal nodules were resected and histologically diagnosed as LPD. Smooth muscle cells in LPD lesions expressed progesterone receptor, while estrogen receptor and luteinizing hormone/chorionic gonadotropin receptor were negative.

Conclusions: LPD should be considered when multiple nodules mimicking dissemination of malignancies are found in the abdominal cavity. In the present case, progesterone may have been involved in the pathogenesis of LPD.

MeSH Keywords: Leiomyomatosis • Progesterone • Receptors, Progesterone • Reproductive History • Thecoma

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Background

Leiomyomatosis peritonealis disseminata (LPD) is a rare condition that is characterized by multiple intra-abdominal nodules composed of the proliferation of smooth muscle cells. LPD was first described by Willson and Peale in 1952 [1], and less than 140 cases have been described in the English medical literature [2]. Most LPD cases arise in women of reproductive age, but a few cases occur in postmenopausal women and in men [2,3]. The majority of cases are clinically benign. LPD results in multicentric nodules in the abdominal cavity that frequently exhibit clinical and radiological symptoms mimicking malignant neoplasms [4]. We herein describe a case of LPD arising in a young parous woman who had a history of laparotomy due to ovarian calcified thecoma.

Case Report

A 24-year-old Japanese nulliparous woman who had experienced secondary amenorrhea for 4 years and breast tenderness for 6 months consulted the gynecologic outpatient clinic at Kansai Medical University Hospital. Her menarche was at 19 years of age, and she had never used oral contraceptives. No family history of disease was reported. At consultation, a hard solid mass was palpated during the gynecologic examination, and pelvic computed tomography (CT) revealed a severely calcified mass measuring 6.6 cm in diameter at the right side of her uterus. Laboratory examination showed no abnormalities in blood count, renal function, or liver function. The patient's serum estradiol was within normal levels (44.6 pg/ml; normal range, 25 to 411 pg/ml), and the serum progesterone level was not measured. She was admitted to the gynecology unit at Kansai Medical University Hospital, and an abdominal ovariectomy was performed. The right ovary was enlarged and weighed 158 g. Normal ovarian tissue was replaced by a widely and severely calcified lesion mixed with focal soft and fatty yellowish areas (Figure 1A). Macroscopically, the patient's uterus and other intraabdominal organs showed no abnormalities. Histologically, the resected ovarian tumor was composed of spindle-to-oval cells with a small number of clearly vacuolated cells (Figure 1B). These spindle cells moved into highly calcified lesions. Sudan III staining revealed fatty droplets in the cytoplasm of clearly vacuolated cells (Figure 1C). The ovarian tumor was histologically diagnosed as a calcified thecoma. After the surgery, the patient's menstrual cycle normalized, and she delivered a healthy boy 5 years later.

One year after the delivery, the patient detected a small nodule in her neck, and the nodule was histologically diagnosed as a leiomyoma. Although she noticed no particular symptoms, a CT scan revealed multiple solid masses in the abdomen and pelvic region. The largest nodule was located in the

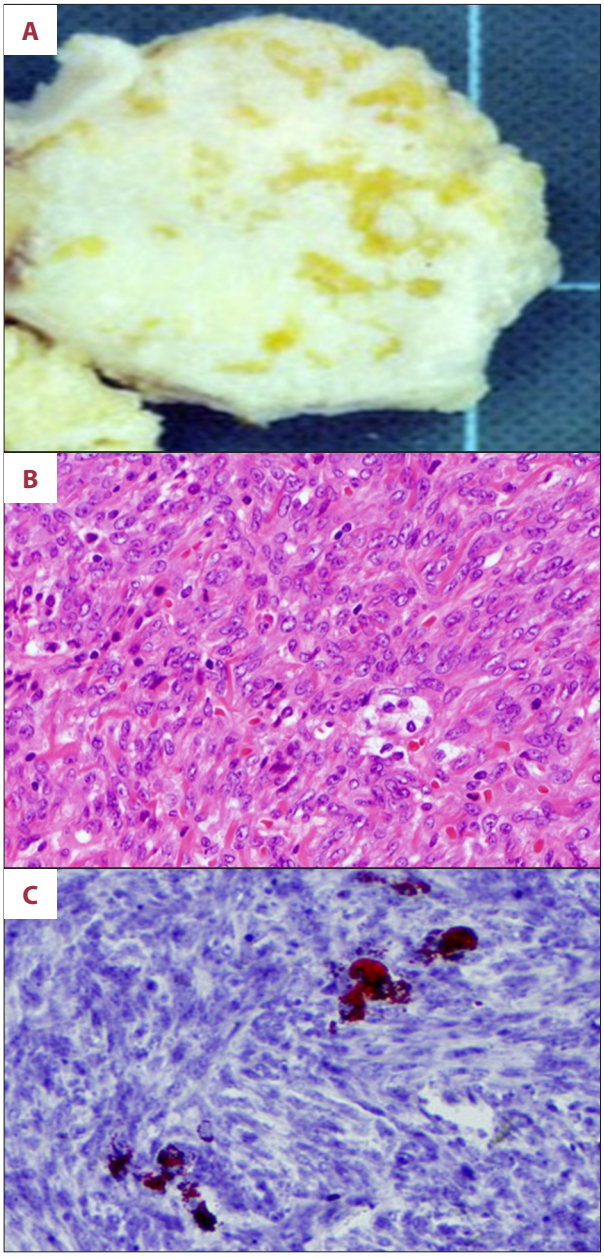


Figure 1. (**A**) Cut surface of calcified thecoma. (**B**) Calcified thecoma. Hematoxylin and eosin (20×). (**C**) Calcified thecoma. Fatty droplets were seen in vacuolated cells. Sudan III (40×).

mesentery of the transverse mesocolon and measured 5.5 cm in diameter (Figure 2). The patient was re-admitted to Kansai Medical University Hospital for the surgical removal of abdominal nodules. According to the operative report, laparotomy revealed multiple coalescent nodules of varying sizes between a few millimeters to 2 or 3 cm. The largest nodule, located in the transverse mesocolon, was removed surgically (Figure 3A), but complete resection of all nodules was impossible because the number of nodules was beyond the resection capacity.

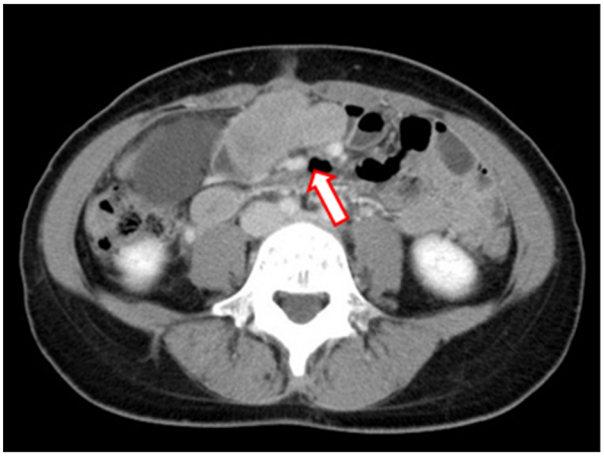
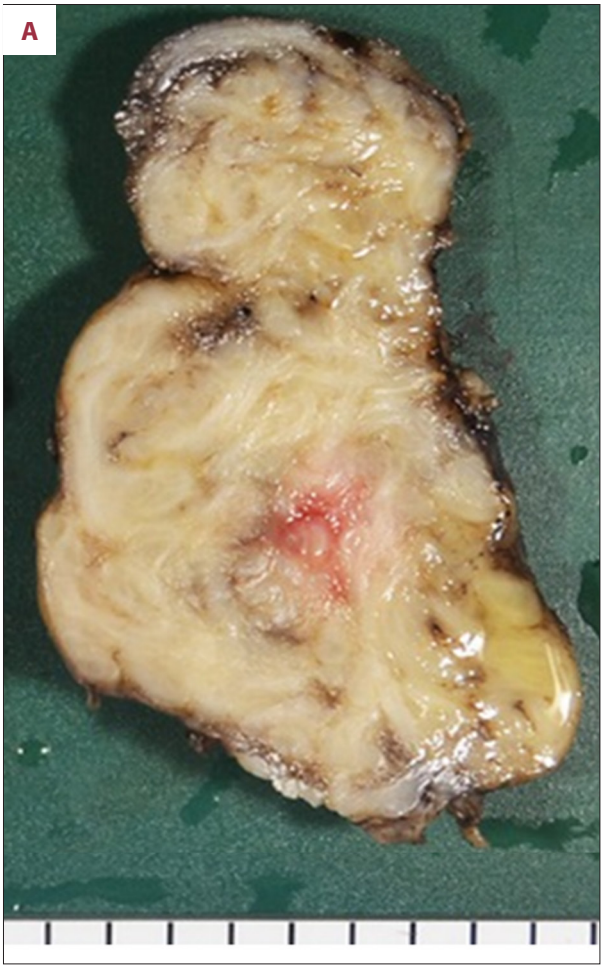


Figure 2. Abdominal CT scan showing intraperitoneal nodules. Arrow in the picture indicates the largest mass in the mesentery of transverse colon.



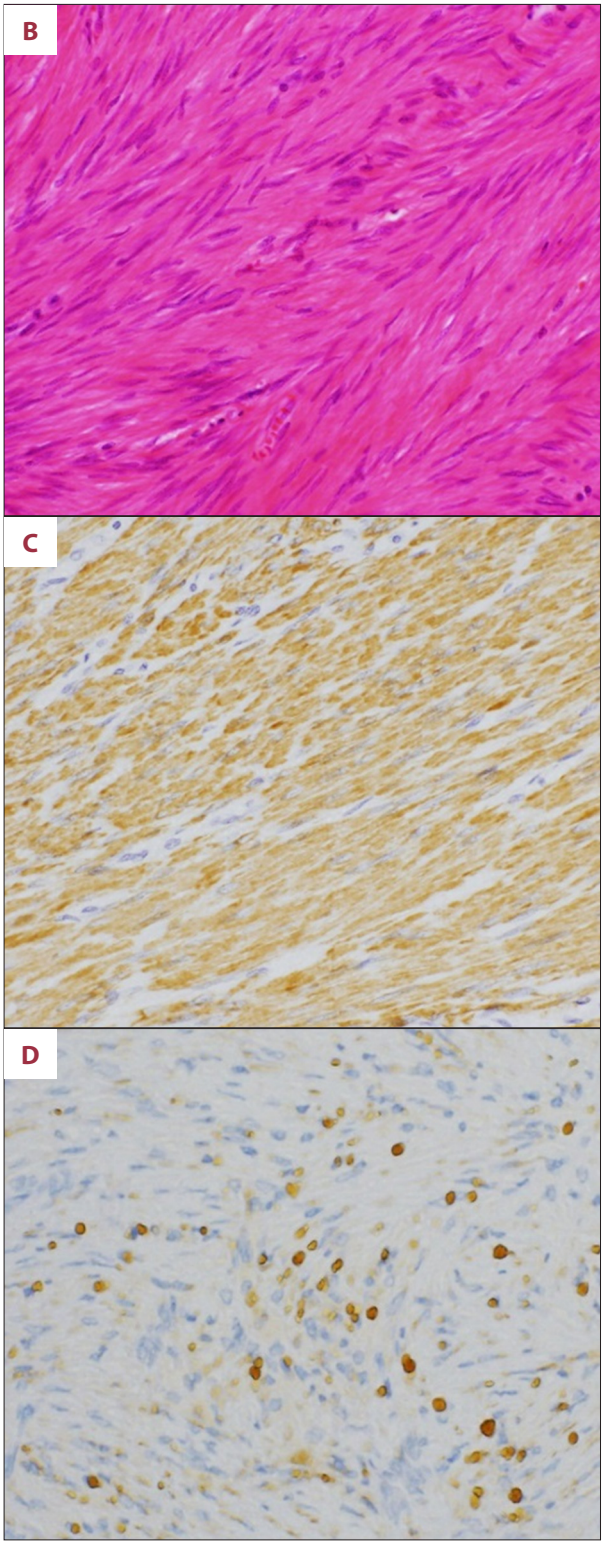


Figure 3. Macroscopic, histologic and immunohistochemical findings of leiomyomatosis peritonealis disseminata (LPD). (**A**) Cut surface of the largest nodule seen in transverse mesocolon. (**B**) LPD is composed of monomorphic spindle cells. Hematoxylin and eosin (20×). (**C**) Spindle cells are positive for desmin (20×). (**D**) Spindle cells are focally positive for progesterone receptor (20×).

The largest nodule that was resected from the mesocolon and the other resected nodules were histologically evaluated. Macroscopically, resected nodules showed no necrosis or hemorrhage. Light microscopy revealed that all nodules were composed of bundles of monomorphic spindle cells. These spindle cells with eosinophilic cytoplasm showed no cytological atypia, and mitotic figures were not detected (Figure 3B). Immunohistochemically, tumor cells were positive for alpha-smooth muscle actin and desmin (Figure 3C) and negative for cytokeratin AE1/AE3, EMA, CD118, and S-100 protein; this staining pattern is typical for smooth muscle tumors [5]. In a few spindle cells, nuclear staining for progesterone receptor was detected (Figure 3D), while estrogen receptor and luteinizing hormone/chorionic gonadotropin receptor were negative (data not shown). Based on these results, the peritoneal nodules were histologically diagnosed as LPD.

The patient's post-operative course was uneventful. After her second laparotomy, the patient remained well and did not report any clinical symptoms. She did not receive any anti-estrogenic compounds. A follow-up pelvic CT scan taken 2 months after the surgery revealed no re-growth of the residual peritoneal nodules.

Discussion

LPD is a rare benign tumor that usually occurs in women of reproductive age. Malignant transformation of LPD has been reported in a few cases [6]. LPD occurs sporadically; however, 1 family cluster with inherited autosomal dominant inheritance has been reported [7]. In a report of 20 women with LPD, 10 patients were pregnant or immediately postpartum, and the other 7 patients used oral contraceptives [8]. LPD has been unexpectedly detected during cesarean section [3]. In addition, there have been 3 reports of LPD in association with steroid hormone – secreting ovarian tumors [1,9,10]; 2 tumors were granulosa cell tumors, and 1 tumor was a fibrothecoma, which resembles our present case. In the previously reported fibrothecoma case, the serum estrogen level was elevated (156 pmol/L), and the gonadotropin levels were suppressed. Although our patient showed no abnormalities in pre-surgical serum estrogen levels, her menstrual cycles normalized after the ovariectomy, which indicates that her resected thecoma was a functioning tumor. In our patient, while LPD cells expressed progesterone receptor, the serum progesterone levels were not measured. However, the development of LPD may be associated with progesterone secretion from the calcified thecoma and/or from the patient's recent pregnancy, which created a high-progesterone environment. Female sex hormones are recognized as an initiator or promoter in the majority of LPD cases.

It is generally accepted that under the influence of endogenous or exogenous female sex hormones, pluripotent mesenchymal stem cells in the peritoneum are capable of metaplastic change into myocytes [9]. These hormonal theories are supported by an experimental study; histologically similar subperitoneal nodules could be reproduced in female guinea pigs by prolonged exposure to estrogen or by combined estrogen and progesterone [11]. However, to date, the pathological spectrum of these peritoneal mesenchymal stem cells has not been determined.

Reports in the literature show that LPD cells frequently express estrogen receptor and/or progesterone receptors [12–14]; progesterone receptor expression is uniform and consistent in LPD cases [15]. Also, luteinizing hormone receptor was detected in LPD cells from a post-menopausal woman who had received tamoxifen therapy for 2 years before the onset of LPD [16]. Particular hormones may bind to their receptors and promote LPD growth. In our case, spindle cell nuclei focally expressed progesterone receptor, while estrogen and luteinizing hormone/chorionic gonadotropin receptors were negative. A few LPD cases are diagnosed in men [17], and some cases do not express hormone receptors. Therefore, factors other than hormones may contribute to the pathogenesis of LPD. In this context, association with endometriosis [18] or iatrogenic causes such as a previous laparoscopic myomectomy or hysterectomy [2] may be included in the etiology. However, the precise etiology and the pathogenesis of LPD are still controversial.

In the present case, the LPD nodules consisted of spindle cells with no cytological atypia, no mitosis, and no necrosis. The LPD cells expressed smooth muscle actin and desmin, which are features of benign smooth muscle cells [5]. To date, clinical consensus in the management of LPD has not been established because of its rarity. One recommended treatment of LPD is surgical tumorectomy if the clinical symptoms such as abdominal distention or discomfort are prominent. Hormone therapies, including ovariectomy and the use of gonadotropin-releasing analogs [19] and aromatase inhibitors, may be effective [20]. Although our patient did not receive hormone therapy, her residual peritoneal nodules did not progress in size, and she did not experience discomfort from the disease.

Conclusions

The pathogenesis of LPD is considered to be related to female sex hormones; the hormonal stimulations target mesenchymal cells in the peritoneum to develop into multiple leiomyoma nodules. Because progesterone receptor was expressed in tumor cells, resected calcified thecoma cells and the previous pregnancy might have elevated the serum progesterone levels, which caused LPD. In female sex hormone receptor – positive cases, hormone therapy may be helpful.

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