Leiomyomatosis Peritonealis Disseminata Associated with Ascites and Endometriosis: a Case Report and Review of the Literature

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Abstract. We present a case of leiomyomatosis peritonealis disseminata (LPD) and review the literature. LPD is a rare, benign disorder that is characterized by multiple subperitoneal or peritoneal nodules of varying sizes on the omentum and peritoneal surfaces, grossly resembling disseminated carcinoma. It should be differentiated from other peritoneal tumors. It is mostly asymptomatic and diagnosis is often incidental during surgery. One should be aware of the iatrogenic component of this entity. LPD is being documented with increasing frequency. We report the case of a 39-year-old woman with chronic abdominal pain and heavy dysmenorrhea due to endometriosis associated with LPD. She underwent an abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy. LPD and endometriosis is a known association. LPD with ascites and endometriosis however has not yet been reported.

Case report

A 39-year-old Caucasian woman, G0P0, had been asymptomatic until a hospital admission for acute abdominal pain that was treated with antibiotics. Afterwards she reported to the gynecologist episodes of vague abdominal discomfort, predominantly on the right side. Her menstrual cycles were regular and she had stopped using oral contraceptives for two years. The vaginal ultrasound examination showed a multicystic area arising from the right ovary. A diagnostic laparoscopy was performed. It revealed adhesions, ascites, a cystic process of the right ovary and nodules on the surface of the omentum. Samples were taken and pathology confirmed the diagnosis of endometriosis, LPD was not described. The follow-up treatment with GnRH agonist lasted 3 months.

She came to our department for a second opinion because of persisting chronic abdominal pain and grade 3 dysmenorrhea. Pelvic examination was normal. Vaginal ultrasound revealed a bilateral multicystic process arising from the ovaries and ascites. Blood analysis was normal except an elevated level of tumor marker ca 125 (112 U/ml : ref 0-35).

Magnetic resonance imaging was performed to rule out malignant disease. It showed hemorrhagic cysts of the ovaries, multiple peritoneal implants suggestive for endometriosis, but no signs of malignancy.

A new diagnostic laparoscopy was performed. It revealed innumerable firm, pale-gray, smooth nodules on the surface of the omentum, ascites and a bilateral multiple cystic process of the adnexal structures with
hemorrhagic fluid. A cystectomy and extensive sampling of the omentum and peritoneum was performed. Histological evaluation demonstrated nodular structures with spindle cells and several endometrial glands. No signs of malignancy were found. These findings are compatible with endometriosis in conjunction with LPD. Immunohistochemically, spindle cells of smooth muscle appearance were positive for desmin, smooth muscle actin, estrogen and progesterone receptors. Some stromal tissue showed features of decidualisation.

Because of persisting complaints not responding to conservative therapy an abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy were performed. Pathology showed areas of endometriosis in the right ovary, normal findings of the left ovary and uterus and confirmed the diagnosis of LPD with endometriosis in the omentum. No signs of malignancy were found.

The patient recovered quick and without complications. One year after surgery the patient was still without symptoms or signs of recurrence.

**Review of the literature : Leiomyomatosis Peritonealis Disseminata**

LPD was first described by Willson and Peale in 1952. In 1965, Taubert clearly delineated the features of the lesions and named this pathologic entity, LPD. It is a rare, benign condition characterized by innumerable smooth muscle nodules throughout the peritoneal cavity. The incidence and the possible pathophysiology of this condition remains unclear. Less than 150 cases of LPD are described in the English literature (15, 16).

**Definition and clinical presentation**

LPD is manifested as multiple, subperitoneal smooth muscle nodules. It is mostly asymptomatic and diagnosis is often incidental during surgery operations like caesarean section, etc. (9). It must be differentiated from other primary peritoneal tumors as primary malignant mesothelioma, multicystic mesothelioma, primary peritoneal serous carcinoma and desmoplastic small round cell tumor (1, 3, 8).

Although many LPD cases have been discovered incidentally during surgery, patients may present abdominal discomfort, abdominal distention, gastrointestinal

![Figure 1. Axial T2 weighted images of hemorrhagic cysts suggestive for endometriosis (white arrow) and central adenomyosis in the uterine body (black arrow).](image)

![Figure 2 A-C.](image)

**Figure 2 A-C.** Showing multiple adnexal cysts (asterix), endometrioma (black arrow) and peritoneal fluid in cavum Douglassi (white arrow). Picture A : T2 weighted image, note typical shading in endometrioma. Picture B : T1 weighted image. Picture C is a T1 weighted fat saturated image which suppresses fat and proves the presence of hemorrhagic content in the cysts.
Complaints, gastrointestinal bleeding and peritonitis following erosion of the LPD implant into the bowel wall and, less commonly, pelvic pain or a palpable mass (e.g., mass effect). When peritoneal masses are discovered, the principal diagnostic concern is metastatic disease, which is the most frequently encountered neoplastic process that involves the peritoneal cavity. Primary peritoneal tumors however, should also be included in the differential diagnosis, particularly when there is no evidence of a visceral primary malignancy. LPD can be suggested as a diagnosis when the patient exhibits coexisting uterine leiomyomas and no evidence of omental cake and ascites (1, 8, 29).

Confusion is possible with benign metastasizing leiomyoma, intravenous leiomyomatosis of the uterus, parasitic myoma or diffuse leiomyomatosis of the uterus (1, 3, 8). A benign metastasizing leiomyoma-like lesion is usually located in a distant location, most commonly the lung. Intravenous leiomyomatosis consists of leiomyoma-like lesions that are found in the pelvic blood vessels and sometimes as far as the heart. A parasitic myoma is usually large and solitary and likely originates as a pedunculated subserosal fibroid which then undergoes torsion from the uterine pedicle and grows freely in the peritoneal cavity by neovascularization from adjacent structures (4, 18, 24).

The majority of LPD cases have been described in premenopausal women, many of whom were pregnant or taking oral contraceptives at the time of diagnosis. LPD however has also been diagnosed in postmenopausal women and even in men (1, 8).

**Imaging**

Cross-sectional imaging studies show numerous well-circumscribed solid masses in the peritoneal cavity that vary in size from several millimeters to many centimeters. The imaging findings will depend on the size and the number of subperitoneal nodules. The difficulty in detecting small peritoneal implants in patients with peritoneal carcinomatosis is well recognized, and the same likely holds true in cases of LPD with numerous small nodules. Sonographic and CT findings include nonspecific solid, and complex soft tissue masses that are often large and mimic a leiomyomatous uterus. If the masses are adjacent to the iliac vessels, they may be confused with lymphadenopathy (1, 8).

The masses are often heterogeneous in CT attenuation and enhance similar to uterine leiomyomas. At MR imaging, the masses of LPD are isointense relative to muscle with T1-weighted sequences and enhance heterogeneously following intravenous administration of gadolinium. With T2-weighted sequences they have low...
signal intensity due to their smooth muscle components. It can be distinguished from endometriotic nodules, as they do not show the T1 hyperintensity characteristic of the latter. However signal intensities on T2 may change depending upon the degree of edema or degeneration. MR features of LPD implants do not differ significantly from features sarcomatous implants. 18F-FDG PET may be used to distinguish isometric activity of LPD from the hypermetabolic uptake of leiomyosarcoma. When making the diagnosis of LPD, it is important to remember that in some cases, multiple, pedunculated leiomyomas arising from the uterus may mimic LPD implants (1, 8, 12, 24).

Pathological features

Grossly, the LPD nodules are firm, well circumscribed, and tan-white with whorl-like trabeculations on the cut surface. The nodules range in size from 0.5 mm to 20 cm and involve a number of structures including the omentum, mesentry, parietal peritoneum, broad ligaments, and surface of the ovary and uterus. There may be tens to hundreds of small nodules. These nodules are located beneath the peritoneum rather than on the peritoneal surface, as occurs with peritoneal carcinomatosis. The histological features of LPD are characteristic of benign uterine leiomyoma because of their composition of closely packed eosinophilic spindle cells in the background of omental or mesenteric adipose tissue. The spindle cells have bland, uniform nuclei and demonstrate increased cellularity, hyalinization, and rare mitotic activity. The smooth muscle cells are markedly reactive for desmin, vimentin and muscle-specific antibodies e.g. alpha-SMA (alpha-smooth muscle actin), but without reaction for keratin and negative for CD34. In most cases the nodules show a high expression of estrogen (ER) and progesterone receptors (PR). This has implications for therapy. Decidual cells have been detected within the nodules in pregnant and postpartum patients. Differentiation sometimes requires electron microscopic examination to distinguish regressing LPD from sarcoma (1, 8, 10, 19, 29, 31).

Etiology and pathogenesis

The possible causes could be divided into iatrogenic, hormonal, subperitoneal mesenchymal stem cell metaplasia, or genetic (1, 4).

In susceptible women who underwent a myomectomy, leaving fragments of myoma in the abdominal cavity might contribute to the development of LPD. A subset of cases of LPD may be secondary to transcervical dissemination of a primary uterine leiomyoma rather than de novo peritoneal metaplasia. Accordingly, one should avoid leaving fragments of the uterus or myoma tissue in the abdominal cavity especially after morcellation e.g. by using an endo-bag. The embolisation of fibroids

Figure 5 A-C. A. Photomicrograph (original magnification, X 20 ; Hematoxylin-eosin (H-E) stain) shows omentum with endometriosis and leiomyomatosis. B. Photomicrograph (original magnification, X 20 ; Estrogen receptor (ER) stain) shows omentum with endometriosis. C. Photomicrograph (original magnification, X 20 ; Smooth Muscle Actin (SMA) stain) shows omentum with leiomyomatosis.

Figure 6. Intraoperative photograph shows innumerable tumor nodules of LPD scattered over the omental surfaces.
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During laparoscopic myomectomy has been cited as more likely to result in seeding than removing intact fibroids (1-5, 12, 17, 24).

The condition is associated with high levels of exogenous and endogenous female gonadal steroids (e.g. pregnancy, prolonged exposure to oral contraceptives or hormonal replacement therapy, granulomatous cell tumors of the ovary,…). This indicates that estrogens and progestins play an important role in the pathogenesis. Excessively more estrogen receptors have been found in the nodules than in normal myometrium. Laboratory experiments with guinea pigs showed similar tumors after having received high doses of estrogen and progesterone. In two subjects LPD developed during tamoxifen use for breast cancer. This selective estrogen receptor modulator has uterine proliferative effects (7, 8, 12, 13, 26, 30).

Developing leiomyomatous nodules could also arise from the Müllerian epithelium, which is distributed throughout the subperitoneal mesenchyme. The smooth muscle nodules are derived from metaplasia of submesothelial cells. It is generally accepted that by appropriate individual predisposition and under the influence of estrogens, pluripotent mesenchymal stem cells are capable of metaplastic change into leiomyocytes, (myo)fibroblasts, endometrial stromal and decidual cells. The primitive mesenchymal stem cell however has never been identified in LPD nodules because of the absence of reliable markers. The subperitoneal localization of the nodules in LPD makes the theory of a metastatic process more unlikely. On clonal molecular and cytogenetic analysis, some authors have suggested that LPD results from implantation and proliferation of benign smooth muscle tissue or cells originating from a uterine myoma. This can also be a result of selection of a clonal abnormality, as takes place in uterine leiomyomas (2, 4, 6, 7).

An abnormality in the X-chromosome and in other chromosomes including chromosomes 17, 12, 8 might imply a common pathogenesis between uterine myoma and LPD. Recently, familial occurrence of LPD has been described, showing an autosomal dominant model with varying degrees of penetrance (2, 4, 6, 7).

Rare cases in postmenopausal women and men have also been reported. These cases suggest an increased tissue sensitivity to normal and diminished levels of estrogen and progesterone. The identification of luteinizing hormone (LH) receptors in LPD nodules from a postmenopausal woman suggests that the typical postmenopausal increase in LH levels might affect the pathogenesis of the disease (7, 8, 12, 30).

Associations

LPD is associated with coexisting uterine leiomyomas. A higher incidence of LPD occur in black women confirming the possible association with uterine leiomyomas (1, 8, 29).

The possible association with endometriosis is suggested in several publications. The origin of these pathologies can be mutual, e.g. a metaplastic transformation of the submesothelial multipotential mesenchymal cells but we also have to mention the existing association of uterine leiomyoma and endometriosis as well (3, 4, 17).

A rare case describes a unique combination of LPD with endocervicosis. The latter is characterized by numerous endocervical-type glands and usually located in the posterior wall or dome of the bladder. In the cystic areas of the nodules in this case, the cavities were lined by endocervical type epithelium and surrounded by a thick wall composed of smooth muscle (20).

2 cases are reported where LPD arose after assisted reproductive technology pregnancy, in which an excess of estrogen produced by ovarian hyperstimulation appears to play a role in the development of the disease. Both cases also had a history of uterine fibroid enucleation. As mentioned above parasitic implantation of fragments of leiomyomas growing in abdominal wall incisions after laparoscopic myomectomy can play a role (12).

Associations of LPD with granulocellular tumor of the ovary, endometrial adenocarcinoma, clear cell carcinoma of the ovary, cystadenofibroma with borderline lesions of the ovary, Brenner tumor and estrogen secreting ovarian fibrothecoma have also been found (13, 27).

No reports of multiple congenital malformations associated with LPD have been proven. One article mentions a possible association with the Currarino syndrome, which is a caudal regression syndrome with a combination of hemisacrum, anorectal malformation, and presacral mass (5).

Malignant transformation

Sarcomatous degeneration may occur though only 10 reports have been published in current literature. At least 7 patients were diagnosed LPD and presented with leiomyosarcoma (LMS) in less than 1 year. None of these patients had been exposed to exogenous estrogens, and none had uterine leiomyomas. 3 of them were postmenopausal. The transformation is characterized by cytologic nuclear atypia, tumor necrosis, infiltrative growth and increased mitotic activity. Two patients demonstrated a rise in ca 125 during recurrence. It remains doubtful whether malignant transformation of LPD occurs. No transformation from benign smooth muscle tissue to malignant LMS tissue has been described within the same nodule. Cases of LPD, without exposure to exogenous or increased endogenous estrogen, without uterine leiomyomas, and without ER and PR expression in the LPD nodules, may represent a...
different entity with a high malignant potential. 2 out of the 10 malignant changes were reported in men (1-3, 8-11).

Therapeutic options

There are no firm guidelines in the literature regarding these patients. The majority have a benign clinical course, with spontaneous regression of the leiomyomas. This can be after delivery, withdrawal of oral contraceptives or following withdrawal of ovarian hormones. One case reports a pregnant woman with massive growth of the tumor nodules who underwent a preterm cesarean section due to increasing abdominal pain. Postpartum a spontaneous regression of the LPD was marked. Gonadotrophin releasing hormone agonists (GnRHa) will shrink the nodules but one case report described a stimulation of tumor growth after GnRHa. Aromatase inhibitors are effective in other conditions that respond well to GnRHa suggesting that it is promising medication for LPD. In published literature one postmenopausal nonresectable LPD patient was successfully treated with aromatase inhibitors. Progestins such as megestrol acetate or a progesterone antagonist such as RU 486 have been advocated as an adjuvant hormonal therapy to accelerate regression of residual tumour and to avoid radical surgery (1-4, 8, 14, 19, 23). Systemic chemotherapy with doxorubicin and dacarbazine may be considered a treatment option for unresectable or metastatic LPD patients (4, 22, 29).

The definitive treatment of symptomatic LPD can call for various surgical procedures. The aetiological association with hormonal stimulation and uterine fibroids may justify total abdominal hysterectomy, bilateral salpingooophorectomy, omentectomy, myomectomy and debulking of the nodules. These procedures have been performed alone or in combination, at primary diagnosis or in recurrence of the disease. Yet, recurrence has been reported after surgical intervention. Extensive debulking of LPD lesions can be required. One case reported a need for colonic resection because of intimate involvement of the large tumor nodules and the rectosigmoid colon (1-4, 8, 14, 28, 29).

Hormonal stimulation seems to play a role in progression of the disease, further use of oral contraceptives, hormonal replacement therapy or additional pregnancies are not recommended after diagnosis of LPD. Menopause should improve the symptoms and reduce progression of the disease. However case reports have shown that it does not give 100 percent guarantee (1-3, 8, 28, 29).

Prognosis

One case reports that in vitro fertilization-embryo transfer can produce a normal mature healthy baby in a patient with LPD who previously underwent an exploratory laparotomy and resection of multiple LPD nodules (21).

Because of the risk of malignant transformation some recommend close surveillance (especially the first years) or aggressive resection in high risk patients mentioned above, postmenopausal women and if there is no need for fertility preservation (1-3, 8, 9, 28).

Recurrence of leiomyoma in LPD is rare but has been reported in several cases (28, 29).

Discussion

Since only described in one other case report the association of LPD with ascites is very rare. These 2 cases show though that the presence of ascites does not exclude LPD from the differentials when abdominal and peritoneal masses are found. As in our case an association of LPD with endometriosis can make diagnosis difficult. The tumormarker ca 125 can be raised. Despite how uncommon the illness is, it should remain in the differentials when patients present with diffuse abdominal pain or an abdominal mass. Extensive surgery is not always necessary but can provide a long-term remission. Preoperative cytologic examination of ascites sample may help to differentiate LPD from malignancy during preoperative evaluation.

The pathological finding of decidualisation in some nodules is unusual because this is normally found in pregnant patients or in woman postpartum. We presented a nulliparous woman with negative HCG blood level. The decidual cells suggest that in this case the LPD arose form metaplasia of Mullarian pluripotent mesenchymal stem cells.

One case report described a stimulation of tumor growth after GnRHa. Also in our patient a treatment with GnRHa was not successful in avoiding recurrence.

Conclusion

LPD is a rare disease and usually follows a benign course. This entity is being reported with increasing frequency. It maybe due to more diagnostic laparoscopy. It is important to be familiar with its presentation, imaging features, differential diagnosis and possible associations. This is the first case report of LPD with ascites without histological features of malignancy associated with endometriosis. An extensive surgical approach was performed successfully without recurrence.

References

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