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A RARE UTERINE TUMOR: DISSEMINATED PERITONEAL LEIOMYOMATOSIS. CLINICAL OBSERVATIONS

Background. Disseminated peritoneal leiomyomatosis (DPL) is an extremely rare benign disease characterized by widespread lesions of the abdominal cavity, pelvis, and retroperitoneal space with tumor nodules of varying size and number, which are benign neoplasms consisting of smooth muscle fibers in their histological structure. **Aim.** To analyze clinical cases of DPL with a concise review of the current state of the DPL diagnosis and treatment. **Materials and Methods.** We analyzed 5 clinical cases of DPL of female patients aged 39—50 years (mean age 46.2 years) who underwent surgical treatment at the National Cancer Institute from 2010 to 2021. In all 5 patients, the diagnosis of DPL (8898/1) was verified according to pathological (using routine hematoxylin/eosin staining) and immunohistochemical (IHC) studies. **Results.** All patients underwent surgical treatment with a laparotomy approach, the extent and radicality of which depended on the location and number of tumor lesions. At the time of follow-up, all 5 patients were alive and did not receive any special oncological treatment. **Conclusions.** DPL is characterized by a variety of clinical manifestations from polyserositis to acute abdomen, depending on the location and size of the main tumor focus. IHC analysis is the criterion for the final diagnosis, and radical removal of all tumor foci provides the best therapeutic prognosis. The treatment should be carried out in highly specialized cancer centers where surgeons have gained sufficient experience in performing cytoreductive surgery.

Keywords: uterine tumor, disseminated peritoneal leiomyomatosis, immunohistochemical analysis, surgical treatment.

In surgical practice, there are cases that clinically resemble a widespread malignant process, according to the data of instrumental and laboratory research methods, look like a disseminated malignant tumor during surgery, which often leads to treatment refusal, but in fact turn out to be a benign disease after pathological and immunohistochemical studies [1—3]. Moreover, in a number of cases, the disease can manifest itself as an acute abdominal clinic, and such

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Table 1. **Peculiarities of DPL cases according to the literature**

Author	Medical history	Patient age	Diagnostics before surgery	Intraoperative diagnosis
Huang et al. [5]	Laparoscopic myomectomy was performed 13 years ago using a morcellator	49	By ultrasound: pathological abdominal and pelvic nodes	Nodes of peritoneum, omentum, mesentery, terminal small intestine
Wu et al. [3]	5 years ago, a laparoscopic myomectomy was performed for chimeric leiomyoma. 2 years later, a Cesarean section was performed without pathological findings	33	By CT scan of the pelvis and omentum: multiple nodules in the pelvis and omentum suspicious for metastatic malignancy	Multiple nodules 1—20 mm in diameter affecting the mesentery of the small intestine, omentum, peritoneum of Douglas' pouch, small intestine serosa, large intestine with invasion of the muscular layer
Momtahan et al. [2]	6 years ago, patient underwent panhysterectomy for a uterine tumor with multiple retroperitoneal nodes, macroscopically resembling a widespread malignant process (histologically — leiomyoma). Patient received HRT	29	By ultrasound: a solid oval mass 79 x 45 mm in the projection of the right appendages, most likely a remnant or recurrence of the previously removed pelvic tumor	A solid tumor with irregular edges and a pseudocapsule was located retroperitoneally adjacent to the external iliac artery
Smirnova et al. [4]	No gynecological operations A childbirth and a medical abortion were in the history	50	Ascites, increase in CA125 to 333.3 U/ml. 2 diagnostic laparoscopies, biopsies of omentum, peritoneum, and ovary. Cytological analysis of ascitic fluid	The omentum was a tumor conglomerate with separate formations of cystic-solid structure 5x6 cm in size. There were multiple disseminations up to 0.3 cm on the parietal peritoneum, tumor formations in the sigmoid colon wall, mesentery of the small and large intestine. The uterus was slightly enlarged. The appendages were unchanged
Askolskaya et al. [6]	Uterine leiomyoma has been diagnosed since 2006. Hysteroresectoscopy with myomectomy was performed in 2010 and 2011. In 2013, during a routine analysis, an ultrasound scan revealed retroperitoneal pelvic masses	40	MRI: multiple masses from 1.6 to 7 cm in diameter, partially with cystic transformation in the pelvic cavity and rectovaginal space	The uterus was of normal size, the appendages were not changed. On the posterior wall of the uterus, there was a 6 cm node on a thin pedicle. Along the course of the right sacrouterine ligament, there were two nodes up to 5 cm; on the pelvic peritoneum in the right round ligament, is a node of 1 cm; in the wall of the ileum, its mesentery, omentum there are multiple nodes up to 6 cm

Table 1. (ending)

Author	Medical history	Patient age	Diagnostics before surgery	Intraoperative diagnosis
Askolskaya et al. [6]	Hysteroresectoscopy was performed 5 times, uterine artery embolization was performed 2 times, laparoscopic myomectomy for uterine cell fibroids was performed 2 times. In 2012, a laparoscopic hysterectomy without appendages was performed	42	The patient was admitted as an emergency with partial intestinal obstruction. Ultrasonography: in the projection of the small intestine there was a mass of reduced echogenicity with clear contours of 4.5 × × 3.6 cm. MRI: a picture of a volumetric small bowel mass, signs of adhesive process of the abdominal organs	Nodules from 0.2 to 4 cm in diameter were found along the peritoneum of the right flank and under the diaphragm. In the omentum, there was a set of nodes from 0.5 to 1.5 cm in diameter. In the mesentery of the small intestine there was a tuberous tumor up to 10 cm in diameter. The uterus was absent. The ovaries were not enlarged, polycystic

patients are admitted urgently to gynecological and surgical general hospitals with suspected torsion of the tumor node or intestinal obstruction [6]. When faced with such cases, the doctors do not understand the tactics of the patient management, despite the fact that the disease is essentially benign and, after a proper treatment, the patient's prognosis is favorable. We are talking about disseminated peritoneal leiomyomatosis (DPL), an extremely rare benign disease characterized by widespread lesions in the abdominal cavity, pelvis, and retroperitoneal space with tumor nodules of varying size and number, which are benign neoplasms consisting of smooth muscle fibers in their histological structure [4]. The disease affects women of the reproductive age and is often associated with the presence of uterine leiomyoma and surgical interventions for it, as well as endometriosis and taking female sex hormone drugs [3, 5]. There are few cases of DPL described in the current literature, and there are no accurate data on the incidence of this pathology in the world (Table 1).

It is important for clinicians to understand that the diagnosis of DPL at the pre-surgical stage is difficult, and the data presented by ultrasound, MRI, CT, and tumor markers (CA-125, HE-4) are nonspecific, because in most cases they describe a widespread tumor process in the abdomen and pelvis, which favors the diagnosis of disseminated ovarian cancer or leiomyosarcoma [1, 4, 5].

There is a wide range of smooth muscle tumors of the uterus to differentiate DPL with (Table 2) [7].

The cause of this disease has not been fully elucidated, but it is believed that the development of leiomyomatosis occurs as a result of metaplasia of stem mesenchymal cells into smooth muscle cells, fibroblasts, myofibroblasts, and decidual cells under the influence of estrogen and progesterone [4].

Materials and Methods

An analysis of 5 clinical cases of DPL in patients who underwent surgical treatment at the NCI from 2010 to 2021 was carried out. In this study, a group of 5 female patients with DPL aged 39—50 years (mean age 46.2 years) was formed. All 5 patients were diagnosed with DPL (8898/1) according to pathological and IHC studies. The features of the clinical manifestation of the disease and anamnestic data of patients are as follows (Table 3).

Histological typing of the tumors was performed using a routine hematoxylin/eosin staining and immunohistochemical analysis.

The monoclonal mouse antibodies used in the study are anti-smooth muscle actin, clone alpha sm-1 (BOND PA0943); anti-human caldesmon, clone h-CD (Dako IS054); anti-vimentin, Clone V9 (BOND PA0640); anti-desmin, clone DE-R-11 (BOND PA0032); anti-estrogen receptor (ER), clone 6F11 (BOND PA0151); anti-Ki-67 antigen, clone MM1 (BOND PA0118); anti-p53, clone DO-7 (BOND PA0057); anti-cytokeratin AE1/AE3 (BOND PA0909); anti-ERG, clone EP111 (Bio SB); anti-CD34, clone QBEnd/10 (BOND PA0212); anti-S-100, clone EP32 (BOND PA0031); anti-anaplastic lymphoma kinase, clone 5A4 (BOND PA0831); anti-CD117, clone EP10 (BOND PA0007); anti-calretinin, and clone CAL6 (BOND PA0346). The standard method of the Novolink Max Polymer Detection System (Leica) was used. Antigen demasking was performed in citrate buffer pH 6.0 at 95 °C. The samples were incubated with primary antibodies at room temperature for 40 min and with secondary antibodies for 30 min. The sections were counterstained with hematoxylin. For the positive control, tissue samples with positive reactivity were used, and for the negative control, the procedure was performed without primary antibodies.

The resulting preparations were examined and photographed using an OLYMPUS BX 46 microscope (Evident, Japan) with a camera and CellSens software under standardized conditions.

Results

All patients received surgical treatment at the National Cancer Institute, Kyiv, Ukraine (Table 4).

The surgery protocol of patient R.V., 49 years old, deserves special attention, as the surgical intervention was performed by a multidisciplinary team with the involvement of a vascular surgeon.

On 31.07.2015, the patient underwent a surgical intervention: removal of retroperitoneal pelvic tumor, resection and reconstruction of the right external iliac vein, and right retroperitoneal lymph dissection. Intraoperative findings: in the pelvis, along the posterior bladder wall, on the right, above the vaginal stump, there was a 10 × × 9 × 11 cm retroperitoneal mass consisting of several components extending to the right parametrium. After separation from the posterior wall of the bladder, the largest two components of the tumor were isolated. The stratified right parametric space, over the external iliac vein and artery, showed a dense 5 × 4.5 cm tumor with invasion into the medial wall of the iliac vein within 4 cm from the confluence. A segment of the external iliac vein was resected, and a 2.8 × 2.5 cm thrombus was removed from the external iliac vein. The postoperative care period was uneventful, and the wound healed with primary tension.

Table 2. **WHO International Classification of uterine smooth muscle tumors, 2014**

Nosological form	ICD-O-code
Leiomyoma	8890/0
Cellular leiomyoma	8892/0
Leiomyoma with bizarre nuclei	8893/0
Mitotically active leiomyoma	8890/0
Hydropic leiomyoma	8890/0
Apoplectic leiomyoma	8890/0
Lipomatous leiomyoma (lipoleiomyoma)	8890/0
Epithelioid leiomyoma	8891/0
Myxoid leiomyoma	8896/0
Delaminating leiomyoma	
Diffuse leiomyomatosis	8890/1
Intravenous leiomyomatosis	8890/1
Metastatic leiomyoma	8898/1
Smooth muscle tumor with uncertain potential for malignancy	8897/1
Leiomyosarcoma	8890/3
Epithelioid leiomyomosarcoma	8891/3
Myxoid leiomyosarcoma	8896/3

Table 3. **Individual manifestations of the disease and some anamnesis data**

Patient, age	Manifestation of the disease	Gynecological history	Somatic history
G.M., 47	Symptoms of right-sided hemorrhagic pleural effusion and ascites	Monthly periods since the age of 11 years, painful for 6—7 days every 25 days. One childbirth and one miscarriage. In 2011, there was extirpation of the uterus without appendages due to leiomyoma combined with endometriosis. In 2013 and 2015, the patient underwent repeated gynecological operations for endometriosis of the vaginal stump and appendages: excision and suturing of the vaginal stump; bilateral adnexectomy.	Varicose veins of lower extremities Chronic colitis
Yu.I., 46	Symptoms of chronic abdominal pain, the patient self-diagnosed the presence of a neoplasm in the abdominal cavity.	Menstruation since the age of 15 years, for 4—5 days every 28 days. One childbirth (cesarean section) and 7 miscarriages Due to genital malformation that was an incomplete uterine septum, the patient underwent excision of the uterine septum, metroplasty. In 2020, the patient underwent laparoscopic removal of ovarian cysts	Chronic gastritis
R.V., 49	Symptoms of chronic pain in the right side of the abdomen. Right-sided pain and external bladder compression	Monthly periods since the age of 12 years. Two childbirths and 5 medical abortions. In 1992, the patient underwent right cystectomy for ovarian cyst. In 2007, the patient underwent extirpation of the uterus with appendages for large uterine fibroids	Varicose veins of lower extremities Chronic gastroduodenitis Chronic pyelonephritis in remission
B.T., 50	Symptoms of acute intestinal obstruction Transversostomy was performed on an urgent basis, according to CT scan of the abdomen and pelvis and MRI of the pelvis, a sigmoid tumor was detected with involvement of the uterus and left appendages	No data available	Bowel polyps
P.A., 39	Abdominal pain during the year, bloating, increase in the volume of the abdomen. Relapse of endometriosis was diagnosed by gynecologist, but because of ascites, the gynecologist-oncologist suspected ovarian cancer and patient was referred to National Cancer Institute where paracentesis was performed. Due to result of cytology of September 16, 2010, separate small clusters of adenocarcinoma elements were obtained. The patient received two courses of chemotherapy (paclitaxel + carboplatin)	Monthly periods since the age of 13 for 4—5 days after 28 days, regular. There were no births or abortions. In 2001, supravaginal amputation of uterus with right appendages was performed due to endometriosis	Varicose veins of the lower extremities Appendectomy in childhood Chronic gastritis

Table 4. **Peculiarities of surgical treatment of patients and verification of diagnosis**

Patient, age	Intraoperative data	Surgery volume	Pathological and IHC studies
G.M., 47	Up to 500 ml of turbid haemorrhagic exudate was in the abdominal cavity; in the loops of the small intestine, omentum, small intestinal mesentery, and subdiaphragmatic space, there were miliary reddish deposits up to 2—3 mm in diameter; in the parietal peritoneum of the pelvis and between the intestinal loops, there were numerous solid cystic fibrous masses from 5 mm to 2 cm in diameter, irregular in shape. The uterus and appendages were absent.	Multiple biopsy of peritoneal heterotopias Omental resection	The phenotype corresponds to a smooth muscle tumor with uncertain malignancy potential (ICD-O code 8890/1), given the history and extent of the process; there is a disseminated peritoneal leiomyomatosis with foci of the type of smooth muscle tumor with uncertain malignancy potential.
Yu.I., 46	In the abdominal cavity was a dense tuberculated neoplasm 20 cm in diameter with a cystic component originating from the large omentum, which is also affected by small disseminations up to 2 cm of similar structure. In the pelvis, multiple dense small disseminations were detected along the pelvic peritoneum in the Douglas space, serous membrane of the uterus, and right fallopian tube; the right ovary was cystically altered, not enlarged. The uterus was not enlarged. The left appendages were absent.	Panhysterectomy Omentectomy Pelvic peritonectomy Resection of the serous membrane of the cecum	Smooth muscle tumor with an uncertain potential for malignancy, which, taking into account clinical data, corresponds to disseminated peritoneal leiomyomatosis (ICD-O code 8898/1).
R.V., 49	In the pelvis, along the posterior wall of the bladder, on the right, above the vaginal stump, there was a peritoneal dense mass 10 x 9 x 11 cm consisting of several components and extending into the right parametrium. The liver, stomach, pancreas, spleen, intestinal loops, and omentum were unremarkable. The uterus and appendages were absent.	Removal of the retroperitoneal pelvic tumor. Resection and reconstruction of the right external iliac vein. Retroperitoneal lymphadissection on the right	The phenotype corresponds to disseminated peritoneal leiomyomatosis (ICD-O code 8898/1)
B.T., 50	There was a significant adhesive process in the abdominal cavity; there were no tumor disseminations in the peritoneum. After viscerolysis, an inflammatory tumor involving the left uterine appendages and mesentery of the sigmoid colon was diagnosed. The uterus and right appendages were unremarkable.	Adnexectomy on the left Transversostomy closure	The phenotype corresponds to disseminated peritoneal leiomyomatosis
P.A., 39	There were massive nodular formations, which were dense, elastic, with clear contours from 0.5 to 3.0 cm in diameter visualized at parietal and visceral peritoneum of small pelvis, peritoneum of small and large intestine, the suspensions of large intestine in the intestinal wall. It was impossible to clearly distinguish the tissue of intestine, mesentery and peritoneum between nodular formations.	Cervix stump extirpation Omentum stump extirpation Pelvic peritonectomy	The phenotype corresponds to disseminated peritoneal leiomyomatosis with diffuse damage to the peritoneum

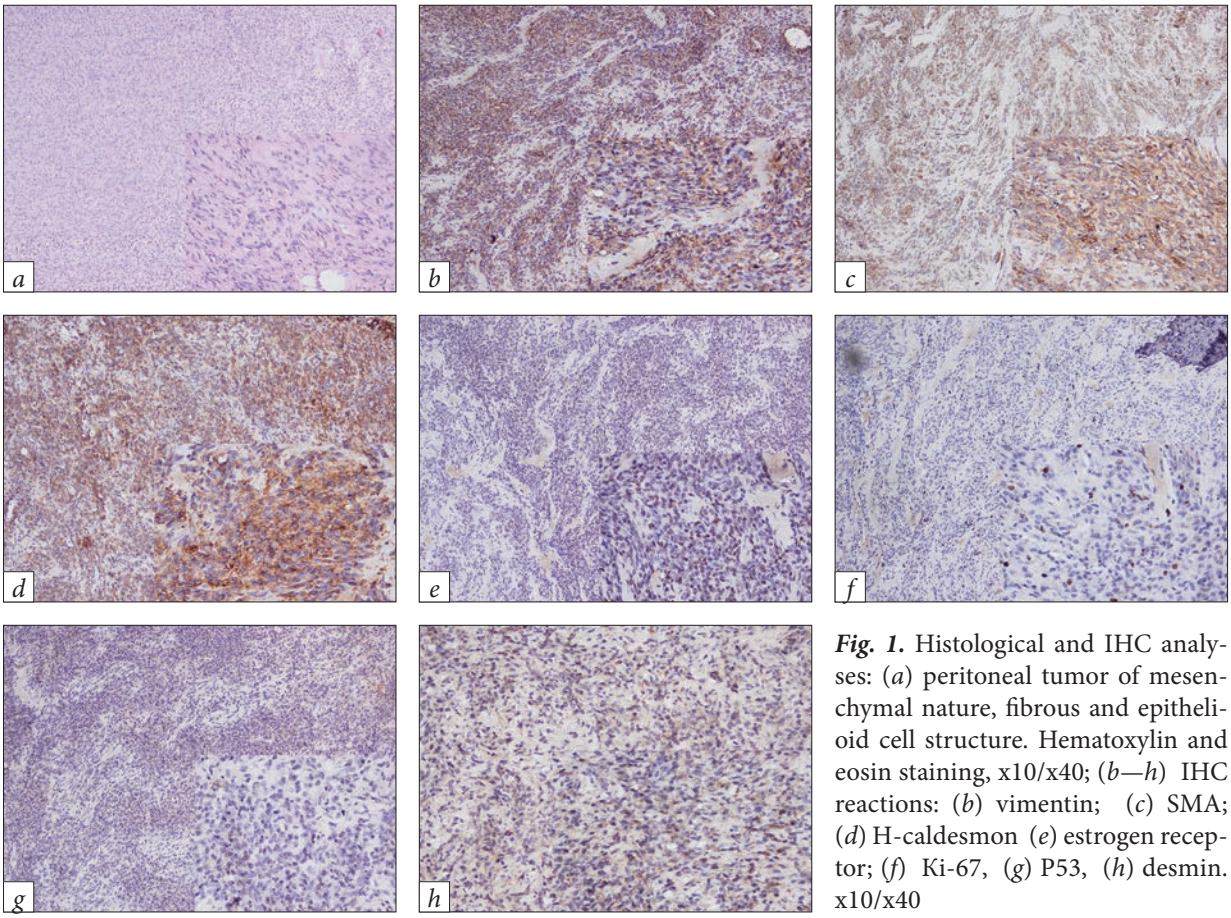

Fig. 1. Histological and IHC analyses: (*a*) peritoneal tumor of mesenchymal nature, fibrous and epithelioid cell structure. Hematoxylin and eosin staining, x10/x40; (*b*—*h*) IHC reactions: (*b*) vimentin; (*c*) SMA; (*d*) H-caldesmon (*e*) estrogen receptor; (*f*) Ki-67, (*g*) P53, (*h*) desmin. x10/x40

Figure shows the results of pathological and immunohistochemical analyses for patient G.M., 49 years old.

All patients were alive at the time of follow-up. One of the five patients had a repeat surgical intervention for peritonitis, and an ileostomy was performed. The rest of the patients did not have any surgical treatment, chemotherapy, or radiotherapy after surgery.

Discussion

Historically, the disease under study was first described by Willson and Peale in 1952 and later defined as DPL by Taubert et al. in 1966 [8, 9]. The etiology of DPL includes several theories, such as hormonal, genetic, and iatrogenic [3]. The disease often occurs after surgery for uterine leiomyoma. The authors describe both conservative myomectomies and radical removal of the uterus, both by open and laparoscopic access [2, 4—6]. Tavassoli and Norris suggest that the tumor process is promoted by the hormonal stimulation, and the detection of the estrogen and progesterone receptor expression confirms this assumption [2, 3, 10]. DPL is most common in the late reproductive [1, 4] and perimenopausal ages [3]. The preoperative diagnosis of DPL is difficult because ultrasound, CT, and MRI data do not always provide comprehensive information about the disease, and myxomatous nodes do not have classic MRI features [6]. The disease is usually manifested as the appearance of multiple nodular masses in the abdominal cavity of various sizes, rarely several or one of large size. Often at the preoperative stage, radiological data

indicate carcinomatosis, and ovarian cancer is suspected because of the presence of ascitic fluid [1, 2, 4, 5]. There is evidence of an asymptomatic course of DPL, its accidental discovery during surgery [6]. During the operation, the detected neoplasms are removed and submitted for urgent histological analysis, which can help diagnose, but the final diagnosis is confirmed after performing definitive paraffin sections [3]. Further histological analysis does not provide a clear answer to the final morphological diagnosis and requires an additional immunohistochemical analysis. It should be noted that the results of the IHC analysis should be interpreted taking into account the morphological and clinical radiological picture, as the differential diagnosis is complex and requires in-depth analysis by a pathologist. The obtained negative reactions with antibodies AE1/AE3, ERG, CD34, Ant S100, ALK, and CD117 allow excluding a number of mesenchymal tumors (GIST, tumors of vascular, neurogenic nature, and others). Combination of positive reactions with antibodies SMA, H-caldesmon, desmin, estrogen, focal p53, and low Ki67 expression, in comparison with the histology and clinical picture, allow us to make a differential diagnosis with smooth muscle uterine and extrauterine tumors, and establish the diagnosis of DPL [1, 11].

With radical surgical removal of all foci of DPL, the prognosis for further life is favorable [1, 4, 6]. The degeneration of DPL into a malignant process is extremely rare but possible [5]. Other authors [1] express a reasonable opinion that DPL is in no way a transitional form between leiomyoma and leiomyosarcoma.

Panhysterectomy, omentectomy, as well as radical removal of all tumor nodes and the use of progesterone preparations are considered an optimal treatment [4, 6]. Other authors suggest the possibility of using gonadotropin-releasing hormone agonists [2, 3, 11]. The overall survival and progression-free survival of these patients have not been thoroughly studied. Further in-depth study of this rare pathology is needed.

Therefore, DPL is a rare benign orphan tumor disease that affects women of late reproductive and perimenopausal ages, and may be associated with the presence of uterine leiomyoma, genital endometriosis in the history, as well as with surgical interventions for these diseases. IHC testing is the main method for making a final diagnosis. Clinical manifestations are diverse and depend on the location of the bulk of the tumor foci (from the picture of polyserositis in the case of small peritoneal and pleural tumor disseminations to the intestinal obstruction and compression of adjacent organs with impaired function in the case of a large solid tumor).

The surgical treatment consists in the radical removal of all tumor foci, which provides the best therapeutic prognosis. Despite the fact that DPL is a benign pathology, patients should receive surgical treatment in highly specialized oncological gynecological centers where doctors have extensive experience in cytoreductive surgery for peritoneal carcinomatosis. Obstetrician-gynecologists and general surgeons are recommended to take a biopsy of tumor lesions in cases of suspected DPL and refer patients to such centers.

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РІДКІСНА ПУХЛИНА МАТКИ: ДИСЕМІНОВАНИЙ
ПЕРИТОНЕАЛЬНИЙ ЛЕЙОМІОМАТОЗ (КЛІНІЧНІ СПОСТЕРЕЖЕННЯ)

Дисемінований перитонеальний лейоміоматоз (ДПЛ) – надзвичайно рідкісне доброякісне захворювання, яке характеризується розповсюдженим ураженням органів черевної порожнини, тазу, заочеревного простору пухлинними вузлами різної величини та кількості, які за гістологічною структурою є доброякісними новоутвореннями, що складаються з гладком'язевих волокон. **Матеріали та методи.** Проведено аналіз 5 клінічних випадків ДПЛ у віці 39—50 років (середній вік 46,2 років). Хворі проходили хірургічне лікування в Національному інституті раку з 2010 по 2021 рік. У всіх 5 пацієнток верифіковано діагноз ДПЛ (8898/1) згідно з даними патогістологічного та імуногістохімічного (ІГХ) досліджень. **Результати.** Усім пацієнткам проведено хірургічне лікування лапаротомним доступом, обсяг та радикальність якого залежали від локалізації та кількості вогнищ пухлинного ураження. Під час катамнестичного спостереження усі 5 пацієнток були живі та в подальшому не отримували спеціального онкологічного лікування. **Висновки.** ДПЛ характеризується різноманітністю клінічних проявів від картини полісерозитів до гострого живота залежно від локалізації та розмірів основного пухлинного вогнища; при цьому ІГХ дослідження є критерієм заключного діагнозу, а радикальне видалення всіх пухлинних вогнищ забезпечує найкращий терапевтичний прогноз. Лікування слід проводити у високоспеціалізованих онкологічних центрах, де хірургами набутий достатній досвід проведення циторедуктивних операцій.

Ключові слова: пухлина матки, дисемінований перитонеальний лейоміоматоз, імуногістохімічне дослідження, хірургічне лікування.