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Leiomyomatosis peritonealis disseminata with aromatase cytochrome P450 expression in a postmenopausal woman: a case study with literature review

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Summary

Purpose of Investigation: The authors aimed to assess the hypothesis that leiomyomatosis peritonealis disseminata (LPD) in a postmenopausal woman had autocrine estrogen secretion abilities. *Materials and Methods:* A 73-year-old woman presented with a bulky tumour in the peritoneal cavity. The pathological diagnosis was LPD or sarcoma of unknown origin. Medroxyprogesterone acetate (MPA) and GnRH analogue therapies were effective, but a tumour mass was confirmed with rapid growth immediately after the cessation of treatment and led to her death from intra-tumour haemorrhage. The authors evaluated the mechanism of tumour using immunostaining for aromatase cytochrome P450. *Results:* The tumour showed high expression of aromatase. The immunostaining patterns of estrogen receptor (ER), progesterone receptor (PgR), and aromatase were similar to those of a premenopausal leiomyoma. *Conclusion:* It is likely that the tumour had the autocrine ability to secrete estrogen and that tumour growth resumed because of a flare-up caused by the downregulation of hormonal therapies.

Key words: Leiomyomatosis peritonealis disseminata; Postmenopause; Malignant, Estradiol; Aromatase immunostaining.

Introduction

Leiomyomatosis peritonealis disseminata (LPD) is an extremely rare disease in which Müllerian duct-derived undifferentiated mesenchymal cells are transformed into multiple smooth muscle nodules in a sub-peritoneal location; however, its etiology has been unclear [1, 2]. It is typically observed in young women and is considered to be particularly associated with conception and sex steroid hormones. It is extremely rare in postmenopausal women; most cases in postmenopause are slowly progressive, and fatal cases are accompanied by malignant transformation. Here, the authors report a case of LPD that developed in a postmenopausal woman and led to death from the hemorrhage of recurrent tumour masses. The tumour had hormonal sensitivity, but a tumour mass with rapid growth was confirmed immediately after the cessation of treatment. The authors evaluated the mechanism of this tumour progress with further histopathological investigation that included immunostaining for aromatase.

Case Report

A 73-year-old Japanese woman (gravida 2 para 2) presented with abdominal distention and weight loss. She had no prior medical history. However, she was diagnosed with diabetes during her first medical examination (glucose 275 mg/dl, HbA1c NGSP 7.3%). Her menopause occurred at 52 years of age, and no menorrhagia after menopause was reported. The patient's body mass index (BMI) was 22.5 (height 152 cm, weight 52 kg). An ultrasound examination revealed the presence of a bulky multilocular mass in the peritoneal cavity and endometrial hypertrophy. A laboratory examination showed the presence of anaemia (Hb 9.8 g/dl, Ht 31.7%), low albumin (TP 6.2 g/dl, ALB 2.9 g/dl) and increased levels of CA125 (163.9 U/ml, normal < 37). Other markers, including LDH, CEA, and CA19-9, were within the normal range. Upper and lower endoscopy demonstrated no specific findings, and diagnostic imaging revealed multilocular solid masses, mainly scattered in the lower abdomen (Figure 1). The authors performed surgery based on the suspicion of an ovarian malignancy. A solid tumour with partial necrosis occupied the peritoneal cavity (Figures 2a, b), and 3,000 ml of hemorrhagic ascites was found upon opening the peritoneal cavity. They identified her uterus and ovaries after extracting numerous masses along the peritoneum. The tumours were macroscopically resected by a total abdominal hysterectomy and bilateral salpingo-oophorectomy after the mass extraction to remove the adhesions.

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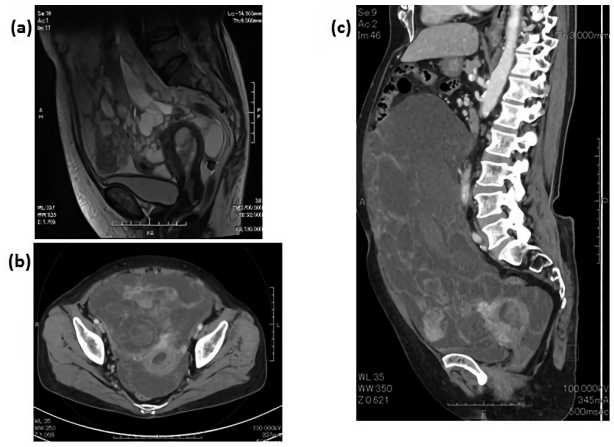

Figure 1. — Diagnostic images prior to the operation: (a) MRI T2 and (b). (c) Contrast CT images of multilocular tumour masses occupying the peritoneal cavity. Endometrial hypertrophy is present.

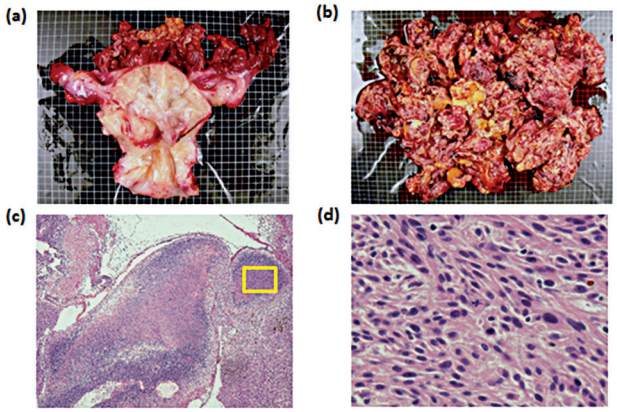

Figure 2. — Macroscopic findings: (a) Uterus and bilateral ovaries. (b) Tumours in the pelvic cavity. (c) Pathological specimens of the tumours. (c) HE ×40. (d) HE ×400. (a) and (b): A laparotomy reveals solid tumours with partial necrosis occupying the peritoneal cavity. (c) The tumours mainly consist of small spindle cells with haemorrhage and necrosis. (d) Karyokinesis is confirmed in a few of the cells at ten high power fields.

surface of the uterus, ovaries with no original tumour inside, and only hyperplasia of the endometrium. The tumours mainly consisted of small spindle cells with bleeding and necrosis. Anisokaryosis was observed in the cells, and karyokinesis was confirmed in a few cells in ten high-power fields (Figures 2c, d). Immunostaining revealed estrogen receptor (ER)-positive, progesterone receptor (PgR)-positive, α-SMA-positive, and CD56-positive cells. The cells were found to be calretinin negative and c-Kit negative, suggesting that mesothelioma and GIST could be ruled out. The authors then considered the possibility of smooth muscle tumours in which the site of the original tumour could not be found and suspected LPD or sarcoma of unknown origin. The serum estradiol (E2) level was 12.7 pg/ml immediately after surgery, followed by a decrease to less than 5 pg/ml one month later. Six months later, it increased to 15.6 pg/ml, and a recurrent tumour mass was observed on the posterior surface of the mesentery (Figure 3). Then, treatment with high-dose medroxyprogesterone

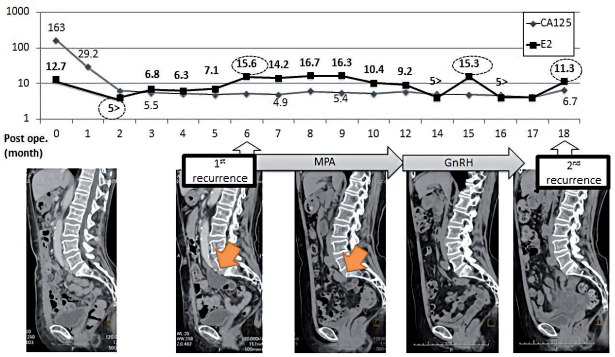

Figure 3. — Postoperative changes in the serum levels of CA125 and E2 as they relate to changes in tumour mass. i) CA125 is elevated prior to the first operation, but remains at a low level despite tumour recurrence. ii) The level of E2 is correlated with changes to the tumour as follows: it decreases to levels below detection two months after the operation, and it increases during the recurrence of the tumour. iii) Images show that the recurrent tumour mass measures 6×5 cm six months after the surgery, and treatment with MPA led to a decrease of the mass, which measures 3×2 cm, with no liquid component, following the treatment. The tumour did not grow for six months, while a GnRH analogue ix given as a maintenance therapy. However, recurrence is found again during a one-month follow-up appointment, resulting in progressive disease.

acetate (MPA) was initiated at 600 mg daily, with the expectation of an anti-estrogen effect. Further evaluation was made based on the levels of E2 and CA125 as serum markers and on diagnostic CT/MRI images. The recurrent tumour mass measured 6×5 cm six months after surgery. Treatment with high-dose MPA decreased the size of the mass to 3×2 cm at 11 months after the surgery. No liquid component was observed. However, the treatment led to the deterioration of the patient's renal function, in part due to her diabetes, and MPA was discontinued. Instead, treatment with a GnRH analogue was initiated as a maintenance therapy. The tumour did not grow for six months following the treatment. However, an abnormal enlargement of the tumour was confirmed during a one-month follow-up appointment, resulting in progressive disease. Although treatment with MPA was resumed, and aromatase inhibitors were administered, the patient died four months after the enlargement of the tumour, 22 months after the first symptoms appeared. She was found to have a blood clotting defect due to an intra-tumour hemorrhage.

Discussion

LPD is an extremely rare disease in which a large number of benign leiomyomas are found in the peritoneal cavity, specifically the peritoneum, mesentery, and greater omentum, rendering the condition clinically malignant. Approximately 160 cases of LPD have been reported in the literature since it was first described in 1952 by Wilson and Peale; however, the etiology has been unclear [3]. LPD occurs when Müllerian duct-derived undifferentiated mes-

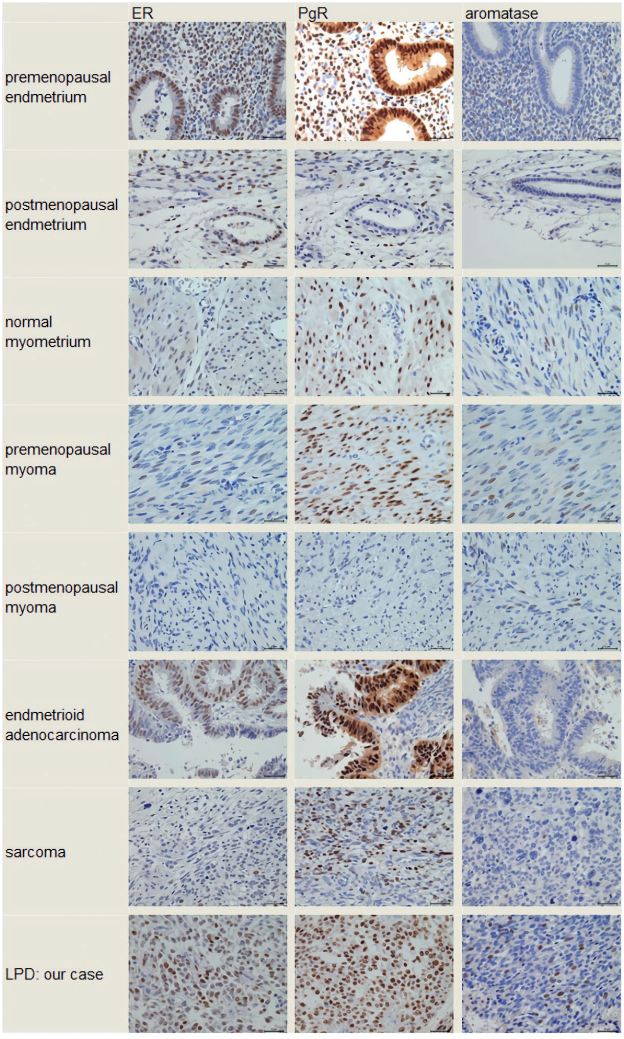

Figure 4. — Immunostaining of ER/ PgR/ aromatase for comparison with normal tissues and tumour tissues. Normal tissues include premenopausal/postmenopausal endometrium and myometrium. Tumour tissues include uterine leiomyoma, endometrioid adenocarcinoma, sarcoma, and the present LPD case.

enchymal stem cells differentiate into smooth muscle cells in a process involving the hormone progesterone in the context of a high-estrogen state [2]. Those stem cells have multipotential abilities and differentiate into specialized epithelia or stroma with Müllerian functions, though they lack fallopian tubes and a uterus. In the present case, the tumours were α-SMA positive, calretinin negative, and c-Kit negative on immunostaining and seemed to be smooth muscle-origin cells of unknown etiology. Previous reports have suggested that the development of LPD may be associated with female sex hormones because many LPD cases are diagnosed during pregnancy or in women with a history of oral contraceptive use [1]. Many cases of LPD have a benign course, typically because decreased exogenous hormonal stimulation, due to either delivery, menopause, adnexa extraction or the termination of treatment with oral contraceptives, leads to LPD regression [4]. However, rare cases of LPD occur in postmenopausal patients or males, in which no clear association between the disease and sex hormones can be found. Butnor *et al*. postulated that the PgR may play a role in the course of postmenopausal LPD [5]. Additionally, cases of LPD without ER or PgR expression in the nodules are regarded as having a high malignancy potential [4, 6]. The prevalence of LPD in postmenopausal women is extremely rare, with only 14 cases reported to date (Table 1 [7-20] and this case), including four cases with malignant transformation [17-20]. An examination of 14 postmenopausal patients revealed that cases with negative ER/PgR tended to have malignant outcomes. Because this case demonstrated positive ER/PgR and a slight increase in estradiol during relapse, this tumour was assumed to have estrogen sensitivity and the authors began estrogen hormone therapy [21, 22]. High-dose MPA was found to shrink tumours, and remission was maintained due to GnRH analogue use; these results suggest the presence of PgRs in recurrent neoplasms that suppress tumour activity by inhibiting estrogen. In the present case, because the relapse occurred after menopause and after ovary removal during the initial therapy, the estrogen expression site became an issue. There are reports of estrogen expression in uterine fibroids [23]; in this case, the authors also used immunostaining with aromatase to assess whether estrogen was expressed from the tumours. Aromatase is a cytochrome P450 enzyme that converts androgen to estrogen; although it exists primarily in the endoplasmic reticulum membrane in gonadal tissue, it is also found in brain and adipose tissue. In breast cancer, there are types of carcinomas that grow in estrogen autocrine or paracrine structures generated from aromatase, therefore aromatase inhibitors are the most important key drugs in breast cancer.

One paper stated that the highest expression of aromatase is observed in the uterine fibroid tissue of African-American women, who have a high rate of uterine fibromas [24]. To compare those findings with this LPD case, the present authors stained and compared ER, PgR, and aromatase in the premenopausal and postmenopausal myometrium, endometrium, uterine leiomyoma, endometrioid adenocarcinoma, and uterine sarcoma tissue (Figure 4). The present authors scored strength of these immunostainings by the Allred score. It consists of an intensity score (3 = strong, 2 = intermediate, 1 = weak, and 0 = none) and a proportion score (0 = none, 1 <1/100, 2 = 1/100 to <1/10, 3 = 1/10 to < 1/3, 4 = 1/3 to 2/3, and 5 ≥2/3). A total score was obtained by adding these scores and ranged from 0 to 8. In Table 2, (-) is scored 0-2, (+) is scored 3-5, and (++) is scored 6-8. Aromatase was expressed in both the myometrium and endometrium in premenopause but was neither observed in postmenopause. Although high expression of aromatase was observed in the present LPD case, these staining pat-

Table 1. – *Fourteen cases of LPD in postmenopausal women, including the present case [refs. 7-20].*

Reference	Age	History of past surgery	Residue after surgery	Malignant transformation	ER/PgR status	Outcome	Complications
Takeda [7]	68	None	Present	No	Positive/positive	Tumour size decreased with Anastrozole treatment	
Kokcu [8]	51	None	None	No	Not performed	No recurrence	
Komatsu [9]	58	43 y. o. hysterectomy for uterine myoma	Present	No	Not performed	No changes to the tumours [two years after operation	
Nigojevic [10]	82	40 y. o. hysterectomy and bilateral salpingo-oophorectomy	None	No	Not performed	No recurrence	Obesity
Strinic [11]	66	None	None	No	Over 50% positive/ 10% positive	No recurrence	
Ngyuen [12] [	63	33 y. o. hysterectomy for menorrhagia	A Few	No	Not performed	No evidence of malignant disease 10 years after operation	
Mansour [13]	54	Hysterectomy for menorrhagia	Present (no operation)	No	Not performed	Very slow progression over several decades	
Brumback [14]	55	43 y. o. laparotomy for peritonitis	None	No	Not performed	No recurrence	Diabetes
Rajab [15]	66	None	None	No	Not performed	No recurrence	
Hiraoka [16]	57	34 y. o. hysterectomy for myoma	Present (cytoreduction)	No	Positive/positive	No progressive changes of the tumours four years after operation	
Raspagliesi [17]	48	None	Present	Yes	Not done	Died	
Tun AM [18]	56	45 y. o. hysterectomy for myoma	Present (leaving small residual masses)	Yes	Negative/negative	Died 5 months after diagnosis	
Sharma [19]	55	47 y. o. hysterectomy for uterine leiomyoma	Present	Yes	negative/negative	Lost to follow-up to undergo further treatment at a different hospital	
Lin YC [20]	50	41 y. o. hysterectomy	Present	Yes	Negative/negative	Died 3 years after diagnosis (chemotherapy was performed)	
Present case	73	None	None (macro-scopically resected)	Unsuspected	Positive/positive	Died 22 months after diagnosis	Diabetes

Table 2. — *Comparison with each tissues in strength of immunostaining of ER, PgR, and aromatase.*

	ER	PgR	aromatase
Premenopausal endometrium	(++)	(++)	(+)
Postmenopausal endometrium	(++)	(++)	(-)
Normal myometrium	(++)	(++)	(+)
Premenopausal leiomyoma	(+)	(++)	(+)
Postmenopausal leiomyoma	(-)	(-)	(+)
endmetrioid adenocarcinoma	(++)	(++)	(-)
Sarcoma	(+)	(++)	(+)
LPD: present case	(++)	(++)	(+)

Allred Score was used which consisted of intensity score (3 = strong, 2 = intermediate, 1 = weak and 0 = none) and proportion score (0 = none, 1 < 1/100, 2 = 1/100 to < 1/10, 3 = 1/10 to < 1/3, 4 = 1/3 to 2/3, and 5= > 2/3). A total score ranged from 0 to 8. In this Table, (-) score 0-2, (+) score 3-5, and (++) score 6-8.

terns were more similar to those of benign premenopausal uterine leiomyoma than those of sarcoma. Considering that E2 fluctuated as the tumour grew and shrank (Figure 4), these results suggest that the tumour was a mass that secreted estrogen. There are reports that GnRH agonist normalizes the levels of aromatase expression in uterine fibroid eutopic endometrium [25], which is consistent with GnRH agonist forcing these tumours into remission. In this case, considering that the tumour re-enlarged when hormone therapy was discontinued, the tumour could have been controlled with continued use of aromatase inhibitors or other treatment.

Conclusion

Here, the authors present a case of LPD in a postmenopausal woman that led to her death from an intra-tumour hemorrhage. The high expression level of aromatase found in the tumours in the present case suggests that the tumours may have expressed estrogen. The mechanism by which LPD occurs in elderly patients, though generally considered to be hormone-dependent, remains unclear; however, these results may contribute to further elucidating this pathology.

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