CASE REPORT

Gemcitabine and docetaxel in a patient with primary ovarian leiomyosarcoma: a case report and review of literature

Yoko Furutake¹ · Tomoyuki Fukagawa¹ · Yasuko Suga¹ · Takayuki Nagasawa¹ ·
Seiya Sato¹ · Hideo Omi¹ · Masahiro Kagabu¹ · Atsumi Chiba¹ · Tadahiro Shoji¹ ·
Satoshi Takeuchi¹ · Tamotsu Sugai² · Hiroaki Itamochi¹ · Toru Sugiyama¹

Received: 27 April 2017 / Accepted: 6 September 2017 / Published online: 11 September 2017
© The Japan Society of Clinical Oncology 2017

Abstract Primary ovarian leiomyosarcoma (POLMS) is extremely rare, and optimal therapy for this disease is unknown. A 40-year-old woman presented at a local hospital with abdominal pain. Tumor resection of the left ovary was performed. The pathological diagnosis was leiomyoma of the left ovary. Nine months after surgery, she developed of severe back pain and a subcutaneous tumor on her left shoulder. Magnetic resonance imaging and computed tomography revealed left ovarian tumor recurrence, pelvic bone metastasis, and multiple liver masses. Biopsy of the subcutaneous tumor on her left shoulder demonstrated metastatic leiomyosarcoma. The previously resected left ovarian tumor was re-examined, and the tumor was found to be a leiomyosarcoma. The patient received gemcitabine 800 mg/m² and docetaxel 60 mg/m² (GD therapy), administered at 3-week intervals. After three cycles of GD therapy, the patient experienced dyspnea and was diagnosed with mild interstitial pneumonia. Oral corticosteroid therapy resulted in complete symptom improvement. Thereafter, the dosage of GD was decreased, and after 13 cycles of GD therapy, radiofrequency ablation was performed twice for liver metastases. The tumors have shrunk by 65.5% after 23 cycles of GD. She remains alive after undergoing 24 cycles of GD. GD therapy may be effective for POLMS.

Keywords Ovary · Leiomyosarcoma · Gemcitabine · Docetaxel · Chemotherapy · Radiofrequency ablation

Introduction

Primary ovarian leiomyosarcoma (POLMS) is a rare disease (approximately 0.1% of all ovarian malignancies) [1]. To our knowledge, only 72 cases of POLMS have been reported [2]. Several studies suggest that the prognosis of POLMS is dismal, especially with residual disease [3–5]. Although standard therapies have not been established, surgery remains the mainstay of treatment, and complete resection should be attempted whenever possible [3–7]. For patients with residual or recurrent disease, chemotherapy may be reasonable treatment, and regimens have been determined according to treatment data for uterine leiomyosarcoma [8]. Here, we confirm that gemcitabine and docetaxel (GD) therapy resulted in obvious reduction in tumor size in our patient with POLMS.

Case report

The patient was a 40-year-old, gravida 5 para 1, Japanese woman who presented at another hospital with abdominal pain. She had no previous medical history, and her family history was unremarkable. Ultrasonography and magnetic resonance imaging (MRI) revealed a 13 × 9-cm intrapelvic mass suspicious of a degenerated uterine leiomyoma (Fig. 1). Her serum lactate dehydrogenase (LDH) level was elevated at 423 IU/L. Diagnosed with uterine leiomyoma, the patient underwent an exploratory laparotomy. The patient had a 12-cm-diameter mass originating from the left ovary. Because she desired fertility preservation, tumor

✉ Hiroaki Itamochi
itamochi@iwate-med.ac.jp

¹ Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, 19-1 Uchimarui, Morioka, Iwate 020-8505, Japan

² Department of Molecular Diagnostic Pathology, Iwate Medical University School of Medicine, 19-1 Uchimarui, Morioka, Iwate 020-8505, Japan

Fig. 1 Preoperative magnetic resonance imaging (MRI) of the pelvic tumor. A tumor measuring 13×9 cm with low signal intensity on T2-weighted MRI was observed anterior to the uterus

resection of the left ovary was performed. The pathological diagnosis of the tumor at that time was leiomyoma of the left ovary. Nine months after surgery, she was referred to our

hospital complaining of severe back pain and a subcutaneous tumor on her left shoulder. MRI and computed tomography (CT) revealed left ovarian tumor recurrence, pelvic bone metastasis, and multiple liver masses.

A biopsy of the subcutaneous tumor on the patient's left shoulder revealed metastatic leiomyosarcoma. Microscopic re-examination of the left ovarian tumor resected at the other hospital revealed spindle cells arranged in fascicles (Fig. 2) with partial nuclear atypia and seven mitotic figures per 10 high-power fields (HPF). Coagulative necrosis was not observed. Immunohistochemical staining of the tumor was positive for smooth muscle actin (SMA) and desmin but was negative for S100, CD34, and c-kit (Fig. 2). The Ki-67 labeling index was 30%. Therefore, the pathological diagnosis was recurrent leiomyosarcoma of the left ovary.

The patient started systemic chemotherapy with gemcitabine 800 mg/m² and docetaxel 60 mg/m² (GD), administered at 3-week intervals. After three cycles, she developed dyspnea. CT revealed interstitial pneumonia with mild ground-glass opacities in her lung. Her dyspnea completely improved after a 5-day course of oral dexamethasone 8 mg/day. Thereafter, the dose of GD therapy was decreased to gemcitabine 400 mg/m² and docetaxel 40 mg/m². After 13 cycles of GD therapy, she achieved an objective tumor response rate of 31.1%, which was a partial response, according to the response evaluation criteria in solid tumors (Fig. 3). She subsequently underwent radiofrequency ablation (RFA) for the treatment of liver metastases twice. The patient has continued outpatient GD therapy and has since

Fig. 2 Microscopic examination of the left ovarian tumor. **a** Tumor cell was composed of spindle cells arranged in fascicles (hematoxylin and eosin staining; magnification, ×100). **b** Enlarged nuclei were observed near the edge of the tumor (hematoxylin and eosin staining; magnification, ×400). **c** Mitotic figures of up to 7 per 10 high-power fields (hematoxylin and eosin staining; magnification, ×400). **d** Immunohistochemistry of the left ovarian tumor. Positive for smooth muscle actin (SMA) and desmin, and negative for S-100 and c-kit

Fig. 3 Computed tomography (CT) scan of the liver (upper panel) and left ovary (lower panel). **a** Before chemotherapy, a large tumor was seen in the right lobe of the liver with a maximum diameter of 12 cm. A left ovarian tumor was also observed. CT scan after the

13th cycle (**b**) and the 23rd cycle (**c**) of gemcitabine and docetaxel (GD) therapy shows definite volume reduction of the liver and left ovarian tumors. The patient also received radiofrequency ablation (RFA) therapy twice after the 13th cycle of GD therapy

received a total of 24 cycles, with tumor shrinkage of 65.5% after 23 cycles of GD therapy (Fig. 3). Severe adverse events have not been observed. She is alive and well 24 months after starting GD therapy.

Discussion

POLMS is extremely rare, and its histogenesis remains uncertain. POLMS probably originates from smooth muscle present in the walls of the blood vessels in the cortical stroma, the corpus luteum, the ovarian ligaments at their point of attachment to the ovary, remnants of the Wolffian ducts, or totipotent cells of ovarian mesenchyme [5, 6].

The diagnostic criteria for POLMS are any two of the following: cellular atypia (or moderate or severe cytological atypia), coagulative necrosis, and mitotic index >10 per 10 HPF [7, 9]. If cellular atypia is present, a mitotic index >5 per 10 HPF can qualify as leiomyosarcoma, regardless of coagulative necrosis [9]. This might be a possible pitfall, because in uterine smooth muscle tumors which are more common than ovarian ones, a diagnosis of leiomyosarcoma is mostly made when mitotic index of the tumor is >10 per 10 HPF. Immunohistochemical staining for POLMS is generally positive for muscle-specific actin, SMA, desmin, and vimentin, and negative for S-100, cytokeratin, and c-kit [5, 7]. In our patient, the tumor was positive for SMA and desmin.

The prognosis for patients with POLMS is thought to be very poor. However, no survival data have been reported because of the rarity of this disease. A literature review of POLMS [1–7, 9–34] revealed 56 cases where data on patient outcomes were available, and survival distribution was calculated by the Kaplan–Meier method. In these patients, 40% patients died within 24 months, with a median survival of 48 months. Moreover, the median survival times for patients with International Federation of Gynecology and Obstetrics (FIGO) stages I, II, and III/IV were 63, 18, and 14 months, respectively. These findings suggest that patients with POLMS have poor outcomes even in the early stages, and prognosis is extremely poor in advanced cases (FIGO stage II or more).

The optimal therapy for POLMS, especially in unresectable cases, also remains unclear. In the literature, the most frequently used adjuvant chemotherapy for POLMS is ifosfamide $\pm$ cisplatin, although the standard chemotherapy regimen has not been established (Table 1) [1–7, 9–34]. Extrapolation of data for the treatment of uterine LMS to the POLMS setting is thought to be reasonable [8]. Recommended regimens for the first-line therapy for uterine LMS include doxorubicin [35], doxorubicin plus ifosfamide [36], gemcitabine [37], and GD [38, 39]. Among these regimens, GD therapy yielded high response rates in uterine LMS. We, therefore, used GD as the first-line chemotherapy in the present case, with favorable results. During GD therapy, our patient underwent RFA therapy for liver metastases, because the tumors were confined to the liver. The effect of

Table 1 Summary of treatment of POLMS in reported patients

Surgery	
TAH ^a + BSO (or USO ^b)	27
BSO (or USO)	17
Omentectomy	13
Lymphadenectomy (pelvic ± para-aortic)	5
Chemotherapy	
IFM	3
IFM + CDDP	2
VCR + DOX (or EPI) + CPA	2
DOX + VCR + 5Fu + CDDP	1
DTIC + DOX + CDDP	1
External RT	4

POLMS primary leiomyosarcoma of the ovary, *TAH* total abdominal hysterectomy, *BSO* bilateral salpingo-oophorectomy, *IFM* ifosfamide, *CDDP* cisplatin, *VCR* vincristine, *DOX* doxorubicin, *EPI* epirubicin, *CPA* cyclophosphamide, *5Fu* fluorouracil, *DTIC* dacarbazine, *RT* radiation therapy

^aSubtotal abdominal hysterectomy: 1 case

^bUnilateral cystectomy: 2 cases

RFA was remarkable and no toxicity was found following the procedure. In soft-tissue sarcomas, especially in gastrointestinal stromal tumors, RFA is used for liver metastases with promising results [40, 41]. To our knowledge, this is the first report that shows a positive response to GD and RFA in a patient with recurrent POLMS. Our patient is alive 24 months after starting GD therapy. Although data about effective treatments for POLMS are limited, GD therapy may be useful for POLMS.

References

- Anderson B, Turner DA, Benda J (1987) Ovarian sarcoma. *Gynecol Oncol* 26:183–192
- He M, Deng YJ, Zhao DY et al (2016) Synchronous leiomyosarcoma and fibroma in a single ovary: a case report and review of the literature. *Oncol Lett* 11:2510–2514
- Monk BJ, Nieberg R, Berek JS (1993) Primary leiomyosarcoma of the ovary in a perimenarchal female. *Gynecol Oncol* 48:389–393
- Piura B, Rabinovich A, Yanai-Inbar I et al (1998) Primary sarcoma of the ovary: report of five cases and review of the literature. *Eur J Gynaecol Oncol* 19:257–261
- Zygouris D, Androustopoulos G, Grigoriadis C et al (2012) Primary ovarian leiomyosarcoma. *Eur J Gynaecol Oncol* 33:331–333
- Rasmussen CC, Skilling JS, Sorosky JI et al (1997) Stage IIIC ovarian leiomyosarcoma in a premenopausal woman with multiple recurrences: prolonged survival with surgical therapy. *Gynecol Oncol* 66:519–525
- Taskin S, Taskin EA, Uzum N et al (2007) Primary ovarian leiomyosarcoma: a review of the clinical and immunohistochemical features of the rare tumor. *Obstet Gynecol Surv* 62:480–486
- Hensley ML, Barrette BA, Baumann K et al (2014) Gynecologic Cancer InterGroup (GCIG) consensus review: uterine and ovarian leiomyosarcomas. *Int J Gynecol Cancer* 24:S61–66
- Lerwill MF, Sung R, Oliva E et al (2004) Smooth muscle tumors of the ovary: a clinicopathologic study of 54 cases emphasizing prognostic criteria, histologic variants, and differential diagnosis. *Am J Surg Pathol* 28:1436–1451
- Kuscu E, Erkanli S, Haberal A et al (2005) Primary ovarian leiomyosarcoma: a case report. *Eur J Gynaecol Oncol* 26:120–122
- Seracchioli R, Colombo FM, Bagnoli A et al (2003) Primary ovarian leiomyosarcoma as a new component in the nevoid basal cell carcinoma syndrome: a case report. *Am J Obstet Gynecol* 188:1093–1095
- Mayerhofer K, Lozanov P, Bodner K et al (2003) Immunohistochemical analysis of a primary ovarian leiomyosarcoma. Case report. *Anticancer Res* 23:3433–3436
- Anderson AE, Yang X, Young RH (2002) Epithelioid angiomylipoma of the ovary: a case report and literature review. *Int J Gynecol Pathol* 21:69–73
- Dixit S, Singhal S, Baboo HA et al (1993) Leiomyosarcoma of the ovary. *J Postgrad Med* 39:151–153
- O'Sullivan SG, Das Narla L, Ferraro E (1998) Primary ovarian leiomyosarcoma in an adolescent following radiation for medulloblastoma. *Pediatr Radiol* 28:468–470
- Nasu M, Inoue J, Matsui M et al (2000) Ovarian leiomyosarcoma: an autopsy case report. *Pathol Int* 50:162–165
- Bodner K, Bodner-Adler B, Czerwenka K et al (2003) Bcl-2 expression in a primary leiomyosarcoma of the ovary: a case report. *Wien Klin Wochenschr* 115:191–195
- Trabelsi A, Mutijima E, El Hossini SA et al (2005) Primary myxoid leiomyosarcoma of the ovary. A case report with review of the literature. *Tunis Med* 83:288–291
- Dobbs SP, Brown LJ, Hollingworth J et al (1999) Surgical treatment of recurrent primary ovarian leiomyosarcoma. A case report. *Eur J Gynaecol Oncol* 20:172–173
- Bouie SM, Cracchiolo B, Heller D (2005) Epithelioid leiomyosarcoma of the ovary. *Gynecol Oncol* 97:697–699
- Arsalan OS, Sumer C, Cihangiroglu G et al (2011) A rare tumor of the female genital tract: primary ovarian leiomyosarcoma. *Arch Gynecol Obstet* 283(Suppl 1):83–85
- Rampaul RS, Barrow S, Naraynsingh V (1999) A primary ovarian leiomyosarcoma with micro-invasive features (stage I): is surgical excision enough? *Gynecol Oncol* 73:464
- Friedman HD, Mazur MT (1991) Primary ovarian leiomyosarcoma. An immunohistochemical and ultrastructural study. *Arch Pathol Lab Med* 115:941–945
- Kurian RR, Preethi J, Remadevi AV (2005) Leiomyosarcoma of ovary—a case report. *Indian J Pathol Microbiol* 48:19–20
- Cortes J, Cuartero ML, Rossello JJ et al (1987) Ovarian pure leiomyosarcoma: case report. *Eur J Gynaecol Oncol* 8:19–22
- Vijaya Kumar J, Khurana A, Kaur P et al (2015) A rare presentation of primary leiomyosarcoma of ovary in a young woman. *Ecancermedscience* 9:524
- Azoury RS, Woodruff JD (1971) Primary ovarian sarcomas. Report of 43 cases from the Emil Novak Ovarian Tumor Registry. *Obstet Gynecol* 37:920–941
- Ansaldi E, Cravero S, Zamburlini S (1986) Primary leiomyosarcoma in preserved ovary after unilateral oophorectomy. *Eur J Gynaecol Oncol* 7:133–134
- Nieminen U, Numers CV, Puroila E (1969) Primary sarcoma of the ovary. *Acta Obstet Gynecol Scand* 48:423–432
- Inoue J, Gomibuchi H, Minoura S (2000) A case of a primary ovarian leiomyosarcoma. *J Obstet Gynaecol Res* 26:401–407
- Nicotina PA, Antico F, Caruso C et al (2004) Primary ovarian leiomyosarcoma. Proliferation rate and survival. *Eur J Gynaecol Oncol* 25:515–516
- Reddy SA, Poon TP, Ramaswamy G et al (1985) Leiomyosarcoma of the ovary. *N Y State J Med* 85:218–220

33. Balaton A, Vaury P, Imbert MC et al (1987) Primary leiomyosarcoma of the ovary: a histological and immunocytochemical study. *Gynecol Oncol* 28:116–120
34. Shakfeh SM, Woodruff JD (1987) Primary ovarian sarcomas: report of 46 cases and review of the literature. *Obstet Gynecol Surv* 42:331–349
35. Omura GA, Major FJ, Blessing JA et al (1983) A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. *Cancer* 52:626–632
36. Sutton G, Blessing JA, Malfetano JH (1996) Ifosfamide and doxorubicin in the treatment of advanced leiomyosarcomas of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol* 62:226–229
37. Look KY, Sandler A, Blessing JA et al (2004) Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) Study. *Gynecol Oncol* 92:644–647
38. Hensley ML, Blessing JA, Degeest K et al (2008) Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. *Gynecol Oncol* 109:323–328
39. Hensley ML, Blessing JA, Mannel R et al (2008) Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol* 109:329–334
40. Pawlik TM, Vauthey JN, Abdalla EK et al (2006) Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. *Arch Surg* 141:537–544
41. Jones RL, McCall J, Adam A et al (2010) Radiofrequency ablation is a feasible therapeutic option in the multi modality management of sarcoma. *Eur J Surg Oncol* 36:477–482