Case Report

Reversion of Hormone Treatment Resistance with the Addition of an mTOR Inhibitor in Endometrial Stromal Sarcoma

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Background. Endometrial stromal sarcomas (ESS) are a subtype of gynaecological sarcomas characterized by the overexpression of hormone receptors. Hormone treatment is widely used in ESS but primary or acquired resistance is common. The mammalian target of rapamycin (mTOR) pathway has been suggested to play a key role in the mechanisms of hormone resistance. Recent studies in breast and prostate cancer demonstrate that this resistance can be reversed with the addition of an mTOR inhibitor. This phenomenon has never been reported in ESS.

Methods. We report the outcome of one patient with pretreated, progressing low grade metastatic ESS treated with medroxyprogesterone acetate in combination with the mTOR inhibitor sirolimus.

Results. Partial response was achieved following the addition of sirolimus to the hormone treatment. Response has been maintained for more than 2 years with minimal toxicity and treatment is ongoing.

Conclusion. This case suggests that the resistance to the hormone manipulation in ESS can be reversed by the addition of an mTOR pathway inhibitor. This observation is highly encouraging and deserves further investigation.

1. Introduction

Sarcomas are a heterogeneous group of more than 50 different malignancies characterized by their poor prognosis and the lack of effective treatments. They can arise anywhere in the body, and the uterus is one of the most common sites [1]. However, uterine sarcomas are rare and they constitute only 1% of female genital cancer and approximately 3–5% of all uterine malignancies [2]. Endometrial stromal sarcomas (ESS) account for approximately 10% of all uterine sarcomas [3] and they characteristically express hormone receptors (HR), that is, oestrogen (ER) and progesterone (PgR) receptors [4]. The expression of ER in ESS ranges between 40 and 80% and PgR is expressed in around 60–100% of cases [5–7]. In addition, ER and PgR expression have been positively correlated with survival in many studies [4, 8, 9]. Furthermore, it is known that uterine cell proliferation and differentiation are regulated in part by hormones. Therefore, the use of oestrogen modulation as an anticancer treatment is a rational therapeutic approach. Although there are no prospective randomised controlled trials of hormonal therapy in uterine sarcomas, a large number of studies have demonstrated its efficacy in ESS [5, 7, 10–13]. Indeed, this therapeutic strategy is widely used given that response rates to chemotherapy are low [14, 15].

ESS are not the only hormone-driven malignancies [16]. Hormones also play a key role in a number of other tumours, especially prostate [17] and breast cancer [18].

The inhibition of the aromatase enzyme in breast cancer has significantly improved the outcome of the patients with HR positive tumours [19–22]. Unfortunately, primary or acquired resistance to hormone treatment is not infrequent. Some studies suggest that this resistance might be mediated through the mammalian target of rapamycin (mTOR) pathway [23–25]. Thus, a study by Baselga et al. demonstrated that everolimus, an mTOR inhibitor, combined with an aromatase inhibitor (AI) significantly improved progression-free survival (PFS) in patients with HR positive advanced breast cancer previously treated with AI [26]. Preclinical studies showed similar results also in prostate cancer [27].
Figure 1: Axial contrast enhanced CT images show a peritoneal deposit within the left side of the abdomen (arrows). Prior to commencing sirolimus, the deposit progressed by RECIST 1.1 over a period of 6 months ((a) and (b)). CT staging at 4 months (c) and 13 months (d) on treatment with sirolimus showed that the deposit had reduced in size but was within the limits of stable disease by RECIST v1.1. A further pelvic deposit (not shown) also reduced in size but overall disease remained stable by RECIST v1.1. However, assessment by Choi criteria which incorporates attenuation changes classified disease status as partial response at 4 months and further partial response at 13 months.

This paradigm of hormone-resistance reversibility observed in breast cancer might be valid in other hormone-driven malignancies as well. We present here the first report ever in which a patient affected by an advanced ESS with a good initial response to hormone treatment benefited from control of her disease following addition of an mTOR inhibitor upon disease progression as defined by RECIST v1.1 [28].

2. Case Presentation

Our patient first presented at the age of 58 years with abdominal pain. A CT scan revealed a 12 cm cystic ovarian lesion. The mass was excised and histopathological analysis showed features consistent with low grade ESS with strong ER and PgR expression. The patient had undergone a total abdominal hysterectomy (TAH) and single oophorectomy 15 years earlier due to a supposed benign condition. Subsequently to the diagnosis of ESS, pathology review of the first operation confirmed low grade ESS. Adjuvant treatment was not prescribed.

Two years following ovarian surgery, the patient presented with right-sided abdominal pain. A new CT scan showed a 5 × 3 cm mass in the inferior pelvis and another mass of similar characteristics in the right iliac fossa. A second operation was performed and the 2 lesions were resected and the pathological analysis demonstrated relapse of her previous ESS with strong HR expression. Postoperative close surveillance and leuprorelin injections, a gonadotropin-releasing hormone (GnRH) analog, were advised. Almost 1 year later, a further relapse in the form of several peritoneal deposits and recurrence of the pelvic mass was diagnosed on a CT scan. The disease was considered unresectable so the patient started treatment with an AI, letrozole 2.5 mg once daily (od). Her disease remained stable for 4 months and the patient did not experience any significant side effects. However, a new CT scan demonstrated progression of her pelvic disease. In addition, the patient reported new abdominal discomfort. A different hormonal manoeuvre was considered and medroxyprogesterone acetate 400 mg od was started. The abdominal symptoms completely disappeared soon after starting treatment in spite of not finding significant tumour changes in regular CT scans, being classified as stable disease (SD) by RECIST v1.1. Moreover, the patient tolerated the treatment well. Nevertheless, progression by RECIST v1.1 in the dominant peritoneal nodule located anteromedial to the splenic flexure was noted after 1 year of treatment: 2.8 cm in maximum diameter compared to 1.4 cm in previous CT scan (Figure 1). The pelvic mass showed no significant changes.

In order to maximize the benefit of the hormone treatment, the mTOR inhibitor sirolimus was added to continuing medroxyprogesterone acetate in an attempt to reverse the hormone resistance. The patient started the new treatment at 3 mg od with a plan to escalate the dose depending on tolerance. However, she developed grade 3 mucositis so had
to reduce the dose to 2 mg od after a short drug holiday. Unfortunately, the mucositis was still intermittently severe so she was recommended to titrate the dose of sirolimus from 1 mg od to 2 mg od depending on toxicity. With this strategy, the patient has been able to tolerate the treatment without symptoms that significantly impair her quality of life. In addition, the imaging assessments have shown renewed control of her disease. Interestingly, the first assessment CT scan performed 4 months after the addition of sirolimus demonstrated a slight reduction in size of the dominant peritoneal nodule from 2.8 cm in maximum diameter to 2.5 cm, being stable by RECIST v1.1. Furthermore, assessment by Choi criteria [29], which incorporates attenuation changes, classified disease status as partial response at 4 months and further partial response at 13 months (Figure 1). In total, the patient has been on sirolimus and medroxyprogesterone acetate for more than 2 years with acceptable tolerance and control of her disease. Her treatment is still ongoing.

3. Discussion

This report suggests for the first time that the resistance to the hormone treatment can be reversed by the addition of an mTOR inhibitor in other tumours apart from breast cancer. This is especially relevant in malignancies like ESS where treatment alternatives are very scarce.

The lack of effective therapeutic options makes ESS a challenging disease [30]. Although ESS tend to have an indolent course, with 5-year disease specific survival of around 90% for stages I-II and 50% for stages III-IV [31], their indolent course, with 5-year disease specific survival demonstrates a challenge for treatment. Although ESS tend to have an indolent course, with 5-year disease specific survival of around 90% for stages I-II and 50% for stages III-IV [31], this is especially relevant in malignancies like ESS where treatment alternatives are very scarce.

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] A. Ferrari, I. Sultan, T. T. Huang et al., “Soft tissue sarcoma across the age spectrum: a population-based study from the surveillance epidemiology and end results database,” Pediatric Blood and Cancer, vol. 57, no. 6, pp. 943–949, 2011.
[2] E. Thanopoulou and I. Judson, “Hormonal therapy in gynecological sarcomas,” Expert Review of Anticancer Therapy, vol. 12, no. 7, pp. 885–894, 2012.
[3] E. D’Angelo and J. Frat, “Uterine sarcomas: a review,” Gynecologic Oncology, vol. 116, no. 1, pp. 131–139, 2010.
[4] R. Koivisto-Korander, R. Butzow, A. Koivisto, and A. Leminen, “Immunohistochemical studies on uterine carcinosarcoma, leiomyosarcoma, and endometrial stromal sarcoma: expression and prognostic importance of ten different markers,” Tumor Biology, vol. 32, no. 3, pp. 451–459, 2011.
[5] M. C. Chu, G. Mor, C. Lim, W. Zheng, V. Parkash, and P. E. Schwartz, “Low-grade endometrial stromal sarcoma: hormonal aspects,” Gynecologic Oncology, vol. 90, no. 1, pp. 170–176, 2003.
[6] X. Cheng, G. Yang, K. M. Schmeler et al., “Recurrence patterns and prognosis of endometrial stromal sarcoma and the potential of tyrosine kinase-inhibiting therapy,” Gynecologic Oncology, vol. 121, no. 2, pp. 323–327, 2011.
[7] D. Pink, T. Lindner, A. Mrozek et al., “Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: Single center experience with 10 cases and
review of the literature," Gynecologic Oncology, vol. 101, no. 3, pp. 464–469, 2006.

[8] S. E. Akhavan, E. Yavuz, A. Tecer et al., "The expression of Ki-67, p53, estrogen and progesterone receptors affecting survival in uterine leiomyosarcomas. A clinicopathologic study," Gynecologic Oncology, vol. 99, no. 1, pp. 36–42, 2005.

[9] Y. J. Ioffe, A. J. Li, C. S. Walsh et al., "Hormone receptor expression in uterine sarcomas: prognostic and therapeutic roles," Gynecologic Oncology, vol. 115, no. 3, pp. 466–471, 2009.

[10] J. Spano, J.-C. Soria, M. Kambouchner et al., "Long-term survival of patients given hormonal therapy for metastatic endometrial stromal sarcoma," Medical Oncology, vol. 20, no. 1, pp. 87–93, 2003.

[11] T. Dahhan, G. Fons, M. R. Buist, F. J. W. ten Kate, and J. van der Velden, "The efficacy of hormonal treatment for residual or recurrent low-grade endometrial stromal sarcoma. A retrospective study," European Journal of Obstetrics & Gynecology and Reproductive Biology, vol. 144, no. 1, pp. 80–84, 2009.

[12] M. Leunen, M. Breugelmans, P. de Sutter, C. Bourgain, and J. J. Amy, "Low-grade endometrial stromal sarcoma treated with the aromatase inhibitor letrozole," Gynecologic Oncology, vol. 95, no. 3, pp. 769–771, 2004.

[13] K. Shoji, K. Oda, S. Nakagawa et al., "Aromatase inhibitor anastrozole as a second-line hormonal treatment to a recurrent low-grade endometrial stromal sarcoma: a case report," Medical Oncology, vol. 28, no. 3, pp. 771–774, 2011.

[14] O. Reich and S. Regauer, "Hormonal therapy of endometrial stromal sarcoma," Current Opinion in Oncology, vol. 19, no. 4, pp. 347–352, 2007.

[15] F. Amant, A. Coosemans, M. Debiec-Rychter, D. Timmerman, and I. Vergote, "Clinical management of uterine sarcomas," The Lancet Oncology, vol. 10, no. 12, pp. 1188–1198, 2009.

[16] K. A. Brown, N. U. Samarajeewa, and E. R. Simpson, "Endocrine-related cancers and the role of AMPK," Molecular and Cellular Endocrinology, vol. 366, no. 2, pp. 170–179, 2013.

[17] G. Attard, J. Richards, and J. S. de Bono, "New strategies in metastatic prostate cancer: targeting the androgen receptor signaling pathway," Clinical Cancer Research, vol. 17, no. 7, pp. 1649–1657, 2011.

[18] I. E. Smith and M. Dowsett, "Aromatase inhibitors in breast cancer," The New England Journal of Medicine, vol. 348, no. 24, pp. 2431–2442, 2003.

[19] J. M. Nabholtz, A. Buzdar, M. Pollak et al., "Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial," Journal of Clinical Oncology, vol. 18, no. 22, pp. 3758–3767, 2000.

[20] J. Bonnerterre, B. Thürlimann, J. F. R. Robertson et al., "Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the tamoxifen or aromide randomized group efficacy and tolerability study," Journal of Clinical Oncology, vol. 18, no. 22, pp. 3748–3757, 2000.

[21] H. Mouridsen, M. Gershovanich, Y. Sun et al., "Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the international letrozole breast cancer group," Journal of Clinical Oncology, vol. 19, no. 10, pp. 2596–2606, 2001.

[22] D. Mauri, N. Pavlidis, N. P. Polyzos, and J. P. A. Ioannidis, "Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis," Journal of the National Cancer Institute, vol. 98, no. 18, pp. 1285–1291, 2006.

[23] R. Schiff, S. A. Massarweh, J. Shou et al., "Cross-talk between estrogen receptor and growth factor pathways as a molecular target for overcoming endocrine resistance," Clinical Cancer Research, vol. 10, no. 1, part 2, pp. 331S–336S, 2004.

[24] S. R. D. Johnston, C. Arteaga, E. Winer, M. Dowsett, R. Kumar, and S. Come, "Clinical efforts to combine endocrine agents with targeted therapies against epidermal growth factor receptor-human epidermal growth factor receptor 2 and mammalian target of rapamycin in breast cancer," Clinical Cancer Research, vol. 12, no. 3, part 2, pp. 1061s–1068s, 2006.

[25] H. J. Burstein, "Novel agents and future directions for refractory breast cancer," Seminars in Oncology, vol. 38, supplement 2, pp. S17–S24, 2011.

[26] J. Baselga, M. Campone, M. Piccart et al., "Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer," The New England Journal of Medicine, vol. 366, no. 6, pp. 520–529, 2012.

[27] C. Thomas, F. Lamoureux, C. Crafter, B. R. Davies, E. Beraldi, and L. Fazli, "Synergistic targeting of PI3K/AKT pathway and androgen receptor axis significantly delays castration-resistant prostate cancer progression in vivo," Molecular Cancer Therapeutics, vol. 12, no. II, pp. 2342–2355, 2013.

[28] E. A. Eisenhauer, P. Therasse, A. Bogaerts et al., "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)," European Journal of Cancer, vol. 45, no. 2, pp. 228–247, 2009.

[29] H. Choi, C. Charnsangavej, S. C. Faria et al., "Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria," Journal of Clinical Oncology, vol. 25, no. 13, pp. 1753–1759, 2007.

[30] P. Reichardt, "Everolimus in hormone refractory prostate cancer progression in vivo," European Journal of Cancer, vol. 45, no. 1, pp. 331S–336S, 2009.

[31] J. K. Chan, N. M. Kawar, J. Y. Shin et al., "Endometrial stromal sarcoma: a population-based analysis," The British Journal of Cancer, vol. 99, no. 8, pp. 1210–1215, 2008.

[32] B. M. Seddon and R. Davda, "Uterine sarcomas—recent progress and future challenges," European Journal of Radiology, vol. 78, no. 1, pp. 30–40, 2011.

[33] R. L. Yamnik and M. K. Holz, "mTOR/S6K1 and MAPK/RSK signaling pathways coordinately regulate estrogen receptor α serine 167 phosphorylation," FEBS Letters, vol. 584, no. 1, pp. 124–128, 2010.

[34] R. L. Yamnik, A. Digilova, D. C. Davis, Z. N. Brodt, C. J. Murphy, and M. K. Holz, "S6 kinase 1 regulates estrogen receptor α in control of breast cancer cell proliferation," Journal of Biological Chemistry, vol. 284, no. 10, pp. 6361–6369, 2009.

[35] G. D. Demetri, S. P. Chawla, I. Ray-Coquard et al., "Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy," Journal of Clinical Oncology, vol. 31, no. 19, pp. 2485–2492, 2013.
[36] S. P. Chawla, A. P. Staddon, L. H. Baker et al., “Phase II study of the mammalian target of rapamycin inhibitor ridaforolimus in patients with advanced bone and soft tissue sarcomas,” *Journal of Clinical Oncology*, vol. 30, no. 1, pp. 78–84, 2012.

[37] S. H. Tirumani, J. P. Jagannathan, K. O'Regan, K. W. Kim, K. M. Krajewski, and N. H. Ramaiya, “Molecular targeted therapies in non-GIST soft tissue sarcomas: what the radiologist needs to know,” *Cancer Imaging*, vol. 13, no. 2, pp. 197–211, 2013.