Gynecologic Oncology Reports 31 (2020) 100512

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Distant recurrence in a patient with polyp-confined stage IA serous endometrial carcinoma treated with adjuvant chemotherapy: A case report and review of literature

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ARTICLE INFO

Keywords:
Uterus
Serous
Metastasis
Adjuvant treatment
Polyp

ABSTRACT

Uterine serous carcinoma is a rare, high-risk histological subtype of endometrial cancer, and use of adjuvant treatment in early stage IA disease is inconsistent, especially when the tumor is confined entirely within an endometrial polyp. We herein present a case of extrauterine recurrence in a 67-year-old female with polyp-confined, stage IA uterine serous endometrial cancer. She underwent comprehensive surgical staging with the pathology returning a 5 cm uterine serous carcinoma confined completely to a 7 cm polyp with negative margins, negative myometrial and lymphovascular space invasion, and twenty-nine negative para-aortic and pelvic lymph nodes. She went on to complete six cycles of adjuvant carboplatin and paclitaxel. She presented with a new pleural effusion approximately 20 months after receiving definitive treatment, and a diagnosis of recurrent, metastatic uterine serous carcinoma was confirmed through cytology. A review of the literature suggests practice patterns involving adjuvant treatment for polyp-confined stage IA uterine serous carcinoma are highly variable. Prospective studies clarifying the utility of adjuvant treatment for polyp-confined disease in comprehensively staged patients, especially pertaining to the impact this pathology has on recurrence risk, are needed for these patients.

1. Introduction

Endometrial cancers are the most common gynecologic malignancy in the United States. Uterine serous carcinoma (USC), a high-risk histological subtype "type II" endometrial cancer represents approximately 10% of endometrial cancers yet portends a significantly poorer prognosis than other subtypes. Adjuvant treatment after comprehensive surgical staging for early stage disease is controversial, though conclusions drawn from limited studies and guidelines from professional societies urge providers to carefully consider systemic therapy irrespective of age or stage (Boruta Ii et al., 2009; NCCN Guidelines, 2019). Despite this many women fail to receive adjuvant therapy (Liang et al., 2016; Chang-Halpenny et al., 2013).

USC involved or confined within endometrial polyps in a comprehensively staged patient are a rarer clinical scenario. Unsurprisingly, balancing treatment morbidity with the disease control and survival benefits of adjuvant chemotherapy in a stage IA polyp-confined aggressive cancer has proven difficult owning to the lack of prospective studies, low incidence, heterogenous adjuvant treatment regimens, and variable recurrence data. Therefore, it is not uncommon for providers and patients to decide upon expectant management for such cases (Liang et al., 2016; Chang-Halpenny et al., 2013). However, here we describe the unusual presentation of a patient B.G. with stage IA polyp-confined USC treated with adjuvant chemotherapy who presented with distant recurrent disease.

2. Case report

In 2016, our then 67-year-old patient presented to her gynecologic oncologist for postmenopausal bleeding and had undergone a work-up resulting in the diagnosis of serous endometrial carcinoma. Her past medical history was notable for colon cancer, status post resection in 2005 with negative genetic testing for microsatellite instability; essential hypertension, and obesity. She has no known first-degree family

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https://doi.org/10.1016/j.gore.2019.100512
Received 10 September 2019; Received in revised form 15 October 2019; Accepted 20 October 2019
Available online 05 November 2019

Table 1
Summary of study characteristics and use of adjuvant treatment in Stage IA polyp-limited uterine serous carcinoma.

Author (Year)	Location & date range	Study population	Stage I (# polyp-limited Stage IA USC)	Comprehensively staged, n (%)[a]	Adjuvant treatment in polyp-limited stage IA patients, n (%)	Recurrence by adjuvant treatment[b], n (%)
Fader et al. (2009)	Multi-institution;1993–2006	Stage I patients who were comprehensively staged with at least 10% USC in pathology	142 (n = 19)	142 (100)	**OBS:** 9 (47.4) **CT ± RT:** 7 (36.8) **RT (WPRT, VBT, both)**: 3 (15.8)	**OBS:** n = 1/19 (5.3)
Kiess et al. (2012)	Single Institution;2000–2009	Stage I-II patients with USC who underwent comprehensive staging, treated w/ carboplatin + paclitaxel and VBT	34 (n = 5)	34 (100)	**CT + VBT:** 5 (100)	**0**
Semaan et al. (2013)	Multi-institution;1992–2011	All patients with USC confined to the endometrium without MMI	44 (n = 11)	Complete: 33 (60) Incomplete/None: 22 (40)[c]	**OBS:** 4 (36.4) **CT:** 4 (36.4) **Unavailable info:** 3 (27.2)	**0**
Chang-Halpenny et al. (2013)	Single institution;1997–2011	Stage IA patients with USC or clear cell carcinoma confined to or involving a polyp	51 (n = 32)	Complete: 32 (63) Incomplete: 10 (20) None: 9 (18)	**OBS:** 41 (80) **CT + RT:** 6 (12) **CT:** 3 (6) **VBT:** 1 (2)[d]	**OBS:** n = 3/32 (9.4)
Hanley, et al. (2016)	Multi-institution;2000–2013	Stage IA patients with USC confined to polyp with no LVSI/MMI	33 (n = 33)	Complete: 3 (9) Incomplete: 27 (82) None: 3 (9)	**OBS:** 11 (33.3) **CT:** 13 (39.4) **RT:** 7 (21.2) **CT + RT:** 2 (6)	**OBS:** n = 3/33 (9) **RT:** n = 1/33 (3) **CT + RT:** n = 2/33 (6)
Liang et al. (2016)	Single institution;1995–2012	Stage IA polyp-limited or endometrium-limited Type II[e] cancers with no LVSI/MMI	85 (n = 49)[f]	85 (100)	**OBS:** 15 (30.6) **CT ± RT:** 22 (44.9) **RT (WPRT or VBT):** 12 (24.5)	**CT + VBT:** n = 2/49 (4.1) **VBT:** n = 1/49 (2)
Mandato et al. (2019)	Multi-institution;2003–2013	All patients with USC confined to or involving a polyp	66 (n = 11)	Complete: 27 (41) Incomplete: 29 (44) None: 10 (15)	**OBS:** 6 (54.5) **CT ± RT:** 5 (45.5)	**OBS:** n = 2/11 (18.2)[g]

Abbreviations: CT, chemotherapy; OBS, observation; LVSI, lymphovascular space invasion; MMI, myometrial invasion; RT, radiation therapy; USC, uterine serous carcinoma; VBT, vaginal brachytherapy; WPRT, whole pelvic radiation therapy.

[a] "Comprehensively staged" defined as hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node assessment (Guidelines, 2019), numbers provided indicate proportions of patients who were comprehensively staged over the total cohort, not just IA polyp-limited disease.

[b] Recurrence by adjuvant treatment is only reported for patients with study-confirmed stage IA polyp-limited disease.

[c] Proportion of comprehensively staged patients for the entire study cohort (n = 55); this study did not stratify staging by stage, though n = 44 were stage I.

[d] This study did not stratify type of adjuvant treatment by polyp-limited versus polyp-involved disease.

[e] Type II cancers include Grade 3 endometroid, serous, clear cell, or high-grade mixed histology.

[f] Of the patients with polyp-limited Stage IA disease, this paper did not specify how many polyp-limited patients were USC histology. Of note, 65.9% of the study's cohort was pure serous histology (Liang et al., 2016).

[g] Both patients who developed a recurrence had not undergone comprehensive staging.

history of colon, breast, ovarian, or endometrial cancers.

In 10/2016, she underwent comprehensive cancer staging with a robotic-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy. Her initial pathology returned a 5 cm high-grade serous carcinoma contained completely within a 7 cm endometrial polyp. Notably, no lymphovascular or myometrial invasion was identified, all margins were negative, and all of the pathologic specimens, including 24 pelvic and 5 para-aortic lymph nodes, were negative for tumor. She was consequently diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IA (T1aN0MX) USC confined to a uterine polyp, and began adjuvant treatment with 6 cycles of carboplatin and paclitaxel, completing her final cycle in 1/2017. In 9/2018, she returned to her gynecologic oncologist with complaints of shortness of breath. A PET scan shortly thereafter noted a new right pleural effusion, and a CA-125 drawn at this time was notable for an increase to 205. She was diagnosed with presumed recurrence and her gynecologic oncologist began salvage treatment with paclitaxel, carboplatin, and bevacizumab. She completed 3 cycles of therapy with moderate toxicity and follow up CT scans of the chest, abdomen and pelvis were performed. These scans were negative for any residual disease, and decision was made for observation, follow-up, and repeat imaging in 3 months. She was also referred to cardiology to rule out cardiac etiologies for the pleural effusion, and was subsequently diagnosed with heart failure and started on the appropriate medications. Her next scan in 2/2019 was suspicious for progression with mediastinal adenopathy, but aspirate samples taken from the lymph node were negative for malignant cells. Again, tumor board advised continued expectant management and follow-up scans in 3 months.

When she returned in 5/2019, her repeat scans noted an enlarging right pleural effusion and a thoracentesis was performed. Cytology returned positive for recurrent metastatic high-grade USC. She proceeded with 3 cycles of carboplatin and paclitaxel administered from 5 to 7/2019, complicated by an infusion reaction to carboplatin, transaminitis, grade 2 neuropathy, and unchanged CA-125 levels - overall poorly tolerated. She is currently receiving single agent bevacizumab with stable disease on recent 10/2019 CT scans.

3. Discussion

The adjuvant treatment of endometrial cancer is determined by stage and uterine factors, with early stage, low risk endometrial cancers not requiring adjuvant therapy (Boruta Ii et al., 2009). Advanced stage or high risk histology frequently require adjuvant therapy in the form of chemotherapy, radiation therapy or both. The presence of lymph node metastasis is the most important prognostic factor for endometrial cancer, thus staging with lymph node evaluation is critical to adjuvant treatment planning. Despite the importance of this information, there is evidence of incomplete staging in routine practice (Mandato et al., 2019). USC is unique from endometrioid histology in that the significance of uterine factors such as depth of myometrial invasion and primary tumor size are less reliable for predicting lymph node metastasis (Boruta Ii et al., 2009). Overall, USC demonstrate higher rates of recurrence and a tendency for distant, extrauterine metastases compared to other subtypes of endometrial cancers (Boruta Ii et al., 2009; Chang-Halpenny et al., 2013). Beyond surgical staging, there is no consensus on standard adjuvant treatment for stage IA USC, and patients are usually treated variably with observation, platinum/taxane-based adjuvant chemotherapy, radiation, or multimodal therapy (Boruta Ii et al., 2009; NCCN Guidelines, 2019). USC confined within an endometrial polyp with comprehensive staging complicates an already controversial treatment paradigm.

A literature review was undertaken to identify outcomes reported in patients with stage IA polyp-limited USC. A literature search was performed by querying PubMed articles published through August 2019 using the search term “uterine AND serous AND polyp,” yielding 66 articles. Titles and abstracts were reviewed to identify publications for a full text review, and bibliographies of included studies were assessed for literature that may have been missed in the initial search. Studies were included if they provided staging information, adjuvant treatment and outcome details for polyp-confined stage IA USC.

Seven investigations were identified as reporting on stage IA, polyp-limited USC, with 160 patients included. Of these, three studies required complete comprehensive staging in their inclusion criteria, while the remaining four reported rates of complete surgical staging ranging from 9 to 63% (Table 1) with about half of the cohort having had complete surgical staging. The study that reported the lowest rate of complete staging required inclusion of an omentectomy, which is generally seen as unnecessary in routine surgical staging of USC given the high sensitivity of a visually negative omentum (Mandato et al., 2019; Gehrig et al., 2019). Adjuvant treatment varied between investigation; 30.6–80% of patients underwent observation only, 6–36% of patients received chemotherapy alone, 12–100% of patients received some form of chemoradiation, and 2–24.5% of patients received radiation therapy alone (Table 1). The proportion of patients receiving chemoradiation is likely inflated, as three of the studies did not differentiate between patients who received radiation in addition to chemotherapy, and one study incorporated receipt of chemoradiation into its inclusion criteria.

Of the patients similar to our patient B.G. with polyp confined, surgically staged USC, thirteen of these patients developed recurrence, with six patients recurring despite receipt of adjuvant treatment

Table 2
Treatment and recurrence details in surgically-staged patients with Stage IA polyp-limited USC.

Study	Adjuvant treatment	DFS	TTR	Location of recurrence
Fader et al. (Fader et al., 2009)	Obs			Extrapelvic
Chang-Halpenny et al. (Chang-Halpenny et al., 2013)	Obs	3.40 yrs	2.87 yrs	Pelvic side-wall
Chang-Halpenny et al. (Chang-Halpenny et al., 2013)	Obs	4.48 yrs	2.71 yrs	Pelvic and abdominal carcinomatosis, ascites
Chang-Halpenny et al. (Chang-Halpenny et al., 2013)	Obs	7.92 yrs	6.83 yrs	Pelvic & retroperitoneal lymphadenopathy, colon implants
Hanley et al. (Hanley et al., 2016)	Obs		62 mo.	Unknown
Hanley et al. (Hanley et al., 2016)	Obs		13 mo.	Unknown
Hanley et al. (Hanley et al., 2016)	Obs		25 mo.	Unknown
Hanley et al. (Hanley et al., 2016)	RT		35 mo.	Unknown
Hanley et al. (Hanley et al., 2016)	CT + RT		26 mo.	Unknown
Hanley et al. (Hanley et al., 2016)	CT + RT		25 mo.	Unknown
Liang et al. (Liang et al., 2016)	CT + VBT		9.9 mo	Lung
Liang et al. (Liang et al., 2016)	VBT		6.4 mo	Mediastinal lymph nodes
Liang et al. (Liang et al., 2016)	CT + VBT		69.8 mo	Hilar and aorto-pulmonary lymph nodes

Abbreviations: CT, chemotherapy; DFS, disease-free survival; mo, months; Obs, observation; RT, radiation therapy; TTR, time to recurrence; USC, uterine serous carcinoma; VBT, vaginal brachytherapy; yrs, years.

[a] “Surgically-staged” patients include any patient who underwent surgical staging, including patients who were completely or incompletely staged.

(Table 2). The recurrence data for the patients cited in the study by Mandato and colleagues was not detailed in Table 2 because these patients had not been surgically staged (Mandato et al., 2019). Additionally, a majority of the patients that did recur presented with extra-pelvic metastases. Recurrence rates among all stage IA patients have been reported ranging from 9.3 to 15.8%, and one study examining USC across all stages failed to find any significant difference in overall survival or progression-free survival between tumors confined to a polyp versus tumors confined to the endometrium (Mandato et al., 2019; Fader et al., 2009; Semaan et al., 2013). The significance of polyp-limited disease in comprehensively staged patients and adjuvant treatment on outcomes in USC represents an important opportunity for future study.

There were several limitations appreciated in our analysis of the included studies. All the sample sizes were small; the largest analysis examined 49 patients with stage IA polyp-limited disease, but this study included clear cell histology (Liang et al., 2016). One additional study also included other high-grade histology in their analysis (Liang et al., 2016; Chang-Halpenny et al., 2013). However all of the chosen studies provided detailed information about recurrence, ensuring the data included in Table 2 was limited to Stage IA, polyp-limited USC. Four studies differed in their reporting of surgical staging; two papers required the inclusion of an omentectomy for comprehensive staging, and the remaining two studies reported only the proportions of their patients who had received a pelvic and/or *para*-aortic lymphadenectomy in addition to their hysterectomy and bilateral salpingo-oophorectomy (Mandato et al., 2019; Semaan et al., 2013; Kiess et al., 2012; Hanley et al., 2016). Finally, the authors acknowledge despite our best attempt to conduct a thorough and comprehensive review of the literature, there may be studies that were overlooked.

4. Conclusion

This case report describes presentation of a patient with stage IA polyp-limited USC who was comprehensively staged with recurrence after adjuvant chemotherapy. A review of the literature demonstrates inconsistent management of patients with polyp-limited stage IA disease, with higher rates of recurrence observed in those who opt for expectant management versus adjuvant treatment, though the statistical significance of this association remains to be seen. Given a majority of the patients in the cohort of interest developed distant metastasis, treating polyp-confined patients as a “lower risk” subgroup of stage IA USC may be a mischaracterization of their disease. While the utility of adjuvant treatment may be controversial, comprehensive surgical staging should be offered to all women with this pathologic finding given the high risk of lymphatic involvement. This review highlights the inconsistent practice patterns and uncertainties that providers are faced with when making difficult treatment decisions with these patients. Quality research is needed to clarify optimal adjuvant treatment for all stage IA USC, and whether the presence of polyp-confined disease should alter management.

Author contribution

Annalyn Welp: Investigation, Writing (Original Draft), Review & Editing; Stephanie Sullivan: Writing, Review & Editing, Supervision, Resources; Sarah Temkin: Review & Editing, Supervision.

Declaration of Competing Interest

We have no conflict of interest to declare.

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