

Pain, An Atypical Presentation of Endometrial Cancer: Case Report and Literature Review

Oroma Nwanodi^{1,*} and Neekianund Khulpatee²

¹Women's Health Department, Myrtle Hilliard Davis Comprehensive Health Centers, - Homer G. Phillips Health Center, 2425 North Whittier Avenue, Saint Louis MO 63113, USA

²Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Maimonides Medical Center, 4802 Tenth Avenue, Brooklyn NY 11219, USA

Abstract: Endometrial cancer, the most common gynecologic malignancy in women in the United States typically presents with abnormal uterine bleeding. Given a case of endometrial cancer presenting as abdominal pain, we reviewed the different circumstances in which pain is the primary presenting symptom of endometrial cancer. Forty-one cases of endometrial carcinoma, were found. Patients presenting with bone pain were statistically significantly more likely to have a longer time to correct diagnosis ($p < 0.001$), and to have metastatic disease than patients presenting with abdominal pain ($p = 0.001$). Abdominal pain was more likely an initial presentation of endometrial cancer ($p = 0.003$), to occur following any radiation treatment ($p = 0.001$), and subsequent to irradiation for cervical cancer ($p = 0.002$), than was bone pain. Nevertheless, 21 of 32 cases (65.6%) of endometrial cancer presenting with pain for which stage is known, have advanced disease, confirming the widely held opinion that pain in endometrial cancer is indicative of advanced stage disease.

Keywords: Abdominal pain, Bone pain, Endometrial cancer, Initial presentation.

1. INTRODUCTION

Endometrial cancer is the fifth most common cancer in women worldwide after breast, cervical, colorectal, and lung and bronchus cancers, with an incidence of about 150,000 cases [1]. In the United States endometrial cancer remains the fourth most common cancer in women after breast, lung and bronchus, and colorectal cancers, with approximately 49,560 new cases and 8,190 deaths estimated for 2013 [2]. The median age at diagnosis of endometrial cancer varies worldwide, but is 60 years in the United States [3]. Endometrial cancer most commonly presents as early stage disease with postmenopausal bleeding or vaginal discharge, although on average, only 10 % of cases of postmenopausal bleeding will actually be due to endometrial cancer [3]. Endometrial cancer should also be excluded in postmenopausal women with pyometria or endometrial cells on cervical cytology, perimenopausal women with increasing menorrhagia or menstrual frequency, or anovulatory premenopausal women with abnormal uterine bleeding [3]. Pain, abdominopelvic pain, low back or lower extremity pain are not found in standard gynecologic oncology texts as a presenting symptom of endometrial cancer [3,4]. However, our literature review and case presentation will show pain to be a presentation worthy of consideration of endometrial cancer.

Endometrial cancer occurring predominantly in obese women with histories of unopposed estrogen has a favorable prognosis [3,4]. Endometrial cancer is more deleterious in women of low body mass index without unopposed estrogen exposure [3,4]. Atypical presenting signs and symptoms of endometrial carcinoma can be ominous. Abdominal pain is indicative of advanced disease – stage III or IV, with surgical stage prognostic of future survival [5]. Smith and Anderson found pain to be significantly more noticeable than vaginal bleeding in late stage disease ($p < 0.05$), than in early stage disease [5]. Smith and Anderson's findings are supported by three additional studies: Krissi *et al.*, Lambrou *et al.*, and Kodama *et al.*, which are discussed further in the conclusion [6-8]. Absence of pain was established in the 1950's to 1970's as a reason for delay in presentation for treatment. Anticipated 5-year survival is as low as 5.3% for stage IV disease, but as high as 90.9% for stage I disease [1,4]. If presenting symptomatology is indicative of surgical stage, then the presenting symptomatology could be indicative of future survival. This case report and review tries to better describe the milieu in which pain is the major presenting symptom of endometrial carcinoma.

2. CASE REPORT

An obese 78 year old woman (gravida 4, para 2022) menopausal at 44 years old, body mass index (BMI) 33, presented with two months of disabling, constant, lower abdominal pain and constipation. The patient

*Address correspondence to this author at the Women's Health Department, Myrtle Hilliard Davis Comprehensive Health Centers, - Homer G. Phillips Health Center, 2425 North Whittier Avenue, Saint Louis MO 63113, USA; Tel: (314) 371-3100 x 6087; Fax: (314) 371-0106; E-mail: o.nwanodi@juno.com, onwanodi@mhdhcc.org

gave a history of a Manchester procedure 17 years prior, and left breast lumpectomy followed by radiation seven years ago. She denied any hormonal or birth control pill usage. Initial evaluation included a negative colonoscopy, normal CA 125 of 22.6 U/mL, and pelvic magnetic resonance imaging (MRI) significant for an endometrial thickness of 11 mm and hydrometra for which she was referred to a gynecologic oncologist. A stenotic os precluded endometrial biopsy. The patient was scheduled for dilation and curettage (D&C), hysteroscopy and cystoscopy. Trabeculations and vesicular gravel were noted on cystoscopy, with negative cytology. A distinct cervix was neither visualized nor palpated intraoperatively. The cul-de-sac was entered in the process of attempting to create a passage into the uterine corpus. D&C and hysteroscopy were not performed.

Postoperative treatment for interstitial cystitis did not ameliorate her pain. Two months post procedure distinct uterine tenderness was noted. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, washings, omental biopsy, and lysis of adhesions were performed. Retroperitoneal fibrosis precluded lymphadenectomy. She was incompletely staged as IIIB, (possible IIIC); grade III, endometrioid adenocarcinoma of the endometrium, with intravascular tumor emboli in broad ligament and vaginal vessels, and foci of adenocarcinoma in the vaginal cuff. Postoperatively four cycles of chemotherapy comprising carboplatin and paclitaxel were followed with pelvic irradiation and cisplatin for 5.5 weeks. The patient was still doing well more than 2 years later. Literature review yielded one case of endometrial adenocarcinoma presenting with abdominal pain in a patient without a prior history of pelvic irradiation [8]. Thus, we chose to perform a systematic literature review of cases of endometrial carcinoma for which pain was the distinguishing initial presenting symptom.

3. DISCUSSION

We conducted a systematic search of the PubMed, and OVID databases for English language articles using the keywords "pain," "abdominal pain," and "endometrial cancer." No articles were found with keywords of "back pain," "pelvic pain," or "chest pain" included in the search parameters. Nor were additional articles found when "initial presentation" or "presentation" were used as search parameters. Additional sources were obtained when reference lists for articles so derived included texts not found by the primary search. Foreign language articles that could

readily be translated by the authors, or with English language abstracts that provided the necessary information were included. Time limitations for publication were not placed. Cases of endometrial stromal sarcoma or leiomyosarcoma were excluded. Uccella *et al.*'s report of referred cases is excluded due to insufficient detail of the patients' initial presentation to the referring providers [9].

The included articles comprise of ten articles yielding 11 cases retrieved from the PubMed database search, and twenty cross-referenced articles yielding 29 cases [10-37]. Our case presented above is also included. All included articles provided clinical presentation, work-up, and final diagnosis, but not necessarily staging details. A total of 41 cases presenting with pain are included. SPSS version 20 (IBM Corporation, Armonk, New York, United States of America) was used to perform analysis of unpaired nominal values, comparison of means, and unpaired t-tests. JavaStat (available free at <http://www.statpages.org/ctab2x2.html>) was used to perform comparisons of proportions using fisher exact test due to small sample sizes. Two-tailed $P < .05$ was considered significant.

4. RESULTS

Table 1 lists 27 cases of endometrial cancer presenting with bone pain [10-34]. Table 2 lists 14 cases of endometrial cancer presenting with abdominal pain [13, 35-38]. Metastatic bone pain not abdominal pain is the more common presentation [10-34]. Twenty-nine cases were presentations resulting in a primary diagnosis of endometrial cancer, nine cases represented recurrent disease, and three cases were of progressive disease. Statistical analysis of data extracted from Tables 1 and 2 is summarized in Table 3. Mean age at presentation with bone pain was 59.08 years, and for abdominal pain was 56.21 years, a non-statistically significant difference with overlapping 95% confidence intervals (CI) of 55.38 to 62.79 years and 49.87 to 62.56 years respectively, $p=0.347$. When only cases in which the reported presentation led to an initial diagnosis are considered, the median age at presentation with bone pain is reduced to 56.92 years, but that for abdominal pain remains unchanged at 56.21 years. Median time to diagnosis for both abdominal pain and bone pain presentations was 3 months. However, mean time to diagnosis differed, at 5.62 months for bone pain, and 2.71 for abdominal pain, a statistically significant difference with $p<0.001$.

Table 1: Endometrial Cancer Presenting with Bone Pain

Author	Age	Prior history	Prior XRT	Presentation	Diagnosis / Time to Correct Diagnosis	Disease State	Stage (if stated)
Kanovitch [10]	50	Hysterectomy for Adenocarcinoma of the uterus	-	Lumbar pain	Metastatic endometrial adenocarcinoma to the lumbar spine / ?	Recurrence	-
Ravault [11]	64	Hysterectomy for endometrial cancer 3 years prior	-	Right foot pain	Metastatic papillary adenocarcinoma to the right scaphoid / 10 months	Recurrence	-
Vanecko [12]	54	Occasional postmenopausal bleeding	-	Pain lower left leg	Metastatic endometrial adenocarcinoma to left fibula and hip / 6 months	Initial	IVB
Fehr [13]	45	Stage IB SCCX	pelvis	Low back pain	Endometrial adenocarcinoma / ?	Initial	IV
Gelberman [14]	64	Well differentiated endometrial adenocarcinoma	pelvis	Left ankle pain	Metastatic well differentiated endometrial adenocarcinoma / 4 months.	Progressive	-
Janis [15]	?	Stage II endometrial cancer 3 years prior	pelvis	Left foot, ankle pain	Metastatic endometrial adenocarcinoma / ? (3 years to bone metastasis)	Recurrence	II
Boidi-Trotti [16]	70	Hysterectomy, adnexectomy for endometrial carcinoma	pelvis	Vertebral pain	Metastatic endometrial adenocarcinoma to the vertebrae / ?	Recurrence	-
Boidi-Trotti [16]	55	Hysterectomy, adnexectomy	pelvis	Abdominal+knee pain	Metastatic endometrial carcinoma to knee /?	Recurrence	-
Damewood [17]	58	-	-	Back pain	Mixed mesodermal tumor / ?	Initial	IIIC
Beller [18]	59	Endometrial adenocarcinoma 9 months prior	-	Pain, swelling left upper leg x 4 weeks.	Metastatic endometrial adenocarcinoma to the left femur / ?	Recurrence	IC G2
Author	Age	Prior history	Prior XRT	Presentation	Diagnosis / Time to Correct Diagnosis	Disease State	Stage (if stated)
Onuba [19]	57	Postmenopausal bleeding	-	Right leg pain	Endometrial carcinoma; pathologic fracture of right tibia, metastasis to both tibia / 1 month	Initial	IVB G3
Litton [20]	55	Stage IA endometrial adenocarcinoma	pelvis	Right ankle pain x 1 year	Moderately differentiated adenocarcinoma – right calcaneus / 1 year (2 years to metastasis)	Recurrence	IA G2
Cooper [21]	59	-	-	Right heel pain x 3 months (calcaneous)	Metastatic poorly differentiated adenocarcinoma consistent with an endometrial primary tumor / 4 months	Initial	IVA G2
Nishida [22]	61	Stage III, Grade I endometrial adenocarcinoma	-	Left ankle pain 1 month after initial diagnosis	Metastatic adenocarcinoma with Squamous metaplasia – left calcaneus / 2 months	Progressive	IIIB GI
Schols [23]	66	Endometrial adenocarcinoma 1.5 years prior	-	Right upper arm pain	Metastatic poorly differentiated endometrial adenocarcinoma to the right humerus / Immediate (18 months to metastasis)	Recurrence	IA G3
Petru [24]	61	-	-	Pain and swelling of the left foot	Metastatic well differentiated endometrioid endometrial adenocarcinoma to the left tarsus / Immediate	Initial	IVB GI
Clarke [25]	55	-	-	Right ankle pain x 10 months	Metastatic endometrial carcinoma to right calcaneus and talus / 11 months	Initial	IVB

(Table 1). Continued.

Author	Age	Prior history	Prior XRT	Presentation	Diagnosis / Time to Correct Diagnosis	Disease State	Stage (if stated)
Malicky [26]	44	-	-	Progressive left knee pain	Moderately differentiated endometrioid adenocarcinoma, left femoral metastasis / 3 months	Initial	IVB G2
Rocha [27]	67	Metastatic endometrial carcinoma	pelvis	Mandibular swelling and pain	Metastatic endometrial carcinoma / Immediate	Recurrence	IVB
Sahinler [28]	67	Undifferentiated endometrial adenocarcinoma	-	Painful, hard abscess-like lesion left foot	Metastatic undifferentiated endometrial adenocarcinoma / Immediate	Progressive	IC G3
Neto [29]	39	Remote history of irregular vaginal spotting	-	Right leg pain	Moderately differentiated endometrial endometrioid adenocarcinoma right ischium / ?	Initial	IVB G2
Manolitsas [30]	76	-	-	Right heel pain, nausea, fatigue	Metastatic endometrial adenocarcinoma to right calcaneus / ?	Initial	IVB G3
Giannakopoulos [31]	68	-	-	Pain, right ischium x 4 months	Well differentiated endometrial endometrioid adenocarcinoma / Immediate	Initial	IVA G1
Uharček [32]	67	-	-	Pain, erythema, swelling of right foot	Metastatic well differentiated endometrioid adenocarcinoma / Immediate	Initial	IV
Kehoe [33]	-	Pelvic pain, pain with ambulation	-	Bone pain	Poorly differentiated carcinoma / Immediate	Initial	-
Kehoe [33]	-	-	-	Bone pain	Primary endometrial cancer/ 8 months	Initial	-
Myriokefalitaki [34]	57	-	-	Right hip pain	Moderately differentiated adenocarcinoma/ 9 months	Initial	IVB G2

G, grade; SCCX, squamous cell carcinoma of the cervix; XRT, irradiation.

Table 2: Endometrial Cancer Presenting with Abdominopelvic Pain

Author	Age	Prior history	Prior XRT	Presentation	Diagnosis / Time to correct diagnosis	Disease State	Stage (if stated)
Fehr [13]	64	Stage IIB SCCX	pelvis	Abdominal pain	Mixed mesodermal / up to 6 months	Initial	I
Fehr [13]	48	Stage IIB SCCX	pelvis	Abdominal pain	Endometrial adenocarcinoma / up to 6 months	Initial	IV
Fehr [13]	54	Stage IB SCCX	pelvis	Abdominal pain	Endometrial adenocarcinoma / up to 6 months	Initial	I
Fehr [13]	55	Stage II? SCCX	pelvis	Abdominal pain	Endometrial adenocarcinoma / up to 6 months	Initial	IV
Fehr [13]	53	Stage IB SCCX	pelvis	Abdominal pain	Endometrial adenocarcinoma / up to 6 months	Initial	IV
Fehr [13]	36	Stage IIB SCCX	pelvis	Abdominal pain	Mixed mesodermal / up to 6 months	Initial	IV
Fehr [13]	47	Stage II? SCCX	pelvis	Abdominal pain	Endometrial adenocarcinoma / up to 6 months	Initial	I
Parkash [35]	69	Stage IB cervical carcinoma about 16 years ago	pelvis	Abdominal pain	Uterine papillary serous carcinoma / ?	Initial	IA

(Table 2). Continued.

Author	Age	Prior history	Prior XRT	Presentation	Diagnosis / Time to correct diagnosis	Disease State	Stage (if stated)
Parkash [35]	64	Stage IB cervical carcinoma	pelvis	Abdominal pain	Uterine papillary serous carcinoma / ?	Initial	IB
Parkash [35]	54	Stage IA cervical carcinoma	pelvis	Abdominal pain	Uterine papillary serous carcinoma / ?	Initial	IB
Parkash [35]	44	Stage IB cervical carcinoma	pelvis	Ascites, abdominal pain	Uterine papillary serous carcinoma / ?	Initial	IV
Powell [36]	56	Severe endometriosis	-	Abdominal pain, dyspareunia, dyschezia, hirsutism	Metastatic androgen-secreting borderline endometrioid tumor / Immediate	Initial	-
Childs [37]	65	Nulligravid,	-	Abdominal pain, constipation	Uterine serous adenocarcinoma / 3 months	Initial	IV
Current Publication [38]	78	Manchester procedure, left breast lumpectomy	chest	Disabling abdominal pain	Metastatic endometrioid adenocarcinoma / 3 months	Initial	IIIB G3

G, grade; SCCX, squamous cell cancer of the cervix; XRT, irradiation.

Table 3: Gynecologic Presentation, Clinical History, Pathologic Findings

	Bone Pain		Abdominal Pain		Difference in means / proportions	95% Confidence Interval (CI)	P value
Mean age at presentation *	59.08 ± 8.782	n=24	56.21 ± 10.984	n=14	-2.866	-9.21 , 3.48	
Standard error	1.793		2.936			t=-.976	0.347
Range	39 - 76		36 - 78			df=13	
95% Confidence Interval	55.38 – 62.79		49.87 – 62.56				
Median age at presentation	59		54.5				
Mean age at presentation of initial diagnosis	56.92 ± 10.218	n=13	56.21 ± 10.984	n=14	0.71		
Standard error	2.834		2.936				
Range	39 - 68		36 - 78				
95% Confidence Interval	50.75 – 63.10		49.87 – 62.56				
Median age at presentation of initial diagnosis	57.00		54.50				
Mean time to diagnosis (months) *	5.62 ± 8.46	n=19	2.71 ± 0.917	n=10	-2.91	-3.57 , -2.25	<0.001
Standard error	1.941		0.290			t= -10.034	
Range	0.1 - 36		0.1 - 3			df=9	
Median time to diagnosis (months)	3		3				
Stage of disease at diagnosis							
Advanced	14		7	n=21	0.212	-0.195 to 0.579	0.283
Early	5		6	n=11			
Totals	19		13	32			
Initial presentation of disease **	13		14	n=27	-0.519	-0.519 to -0.152	0.003
Recurrence / progression	12		0	n=12			
Totals	25		14	39			
Metastatic disease **	24		7	n=41	0.774	0.246 to 0.774	0.001
Non-metastatic disease	0		6	n=6			
Totals	24		13	37			

(Table 3). Continued.

	Bone Pain	Abdominal Pain		Difference in means / proportions	95% Confidence Interval (CI)	P value
Prior radiation **	7	12	n=19	-0.541	-0.701 to -0.208	0.001
No prior radiation	20	2	n=22			
Totals	27	14	41			
Prior radiation for cervical cancer **	1	11	n=12	-0.774	-0.980 to -0.212	0.002
Prior Radiation for other cancer	6	1	n=7			
Totals	7	12	19			

Diagnosis of Advanced Stage Disease	Overall = 21	Mean age = 56.67	n=23	95%CI 51.49 – 61.84
Early disease	Overall = 10	Mean age = 59.70	n=12	95% CI 54.52 – 64.88
	19	16	35	

*Comparison of means analysis by one sampled t-test ** Analysis by Fisher exact test.

Clearly, it is biologically plausible that bone pain be indicative of bone metastases, by definition advanced disease, as occurred in the cases presented above, $p=0.001$. Almost three-quarters the cases of bone pain with known stage represented stage 3 or 4 disease (14 of 19, or 73.68%), but only seven of 13 cases (53.85%) of abdominal pain for which stage is known represented advanced disease which was not statistically significant given $p=0.283$. Nevertheless, this amounts to 21 of 32 cases (65.6%) overall, surgically staged as advanced disease.

Of interest, in 11 of 12 cases (91.67%) presenting with abdominopelvic pain, the patients had previously received pelvic irradiation for stage IA – IIB cervical carcinoma [13-16,20,27] whereas, only one of seven cases (14.29%) of bone pain with prior radiation followed irradiation for cervical cancer [13,35,38]. Thus, an abdominopelvic pain presentation of endometrial cancer is statistically significantly more likely to follow a previously irradiated cervical cancer than is a bone pain presentation of endometrial cancer, $p=0.002$.

5. CONCLUSION

Our case, initially diagnosed with metastatic disease within three months of her initial presentation, is consistent with metastatic disease in seven of 13 cases for which stage is known (53.85%). Being 78-years-old with a BMI of 33 our case is also an expected presentation of endometrial cancer: obese, with unopposed estrogen, and older than 60-years-old.

That bone pain is significantly more likely to represent advanced disease is both biologically

plausible and attributable to differing approaches of evaluating bone and abdominal pain. When patients present with bone pain, initial evaluation may focus on a given bone or extremity, rather than the patient as whole [33,34]. If initial bone imaging or bone biopsy does not directly suggest an endometrial etiology, the patient receives treatment for the bony ailment, and may only receive a correct diagnosis upon subsequent reevaluation with more extensive radiographic imaging [33,34]. Whereas, with abdominal pain, imaging of the abdomen and pelvis immediately ensues, promptly revealing a pelvic mass for further evaluation. Therefore, the delayed time to diagnosis when bone pain is the presenting symptom, contributing to the statistically significant difference in time to diagnosis between bone pain and abdominal pain presentations can be rationalized.

Pain as a distinct presenting symptom of endometrial carcinoma in the absence of bleeding is more likely to be bone pain than abdominopelvic pain (27 of 41 cases 65.85%). Twenty-two of 33 staged cases (66.67%), presenting with pain represented advanced disease. This finding concurs with those of Krissi *et al.*, Lambrou *et al.*, Kodama *et al.*, and Pothuri *et al.* [6-8,39].

Krissi *et al.*'s 1996 study of 181 patients with endometrial cancer showed that while only 3.9% of the patients presented with abdominal pain, such patients were statistically significantly more likely to have advanced stage disease ($p<0.01$) and to have a reduced survival when compared to those presenting

with postmenopausal or irregular bleeding [6]. Clearly, there is an association between presentation with pain and advanced stage disease. Lambrou *et al.* in 2004 found that 25% of patients with Stage III and IV disease presented with abdominal symptoms [7]. Lambrou *et al.* also showed a significantly greater proportion of patients presenting with abdominal symptoms to have advanced stage disease ($p < 0.001$), with a 5-year survival of 57.1% as opposed to 67.1-98.4% for early stage disease [4,7]. These findings are supported by Kodama *et al.*'s 2005 study of 242 Japanese women with surgically staged endometrial cancer, in which 10.3% of patients presented with lower abdominal pain and had statistically significant higher FIGO staging ($p < 0.0001$). Cox multivariate analysis showed lower abdominal pain to be an independent prognostic factor for overall survival [8]. Kodama *et al.* also found that patients presenting with pain were more likely to have intraabdominal metastases and more penetrative disease with uterine enlargement, suggesting that pain is a manifestation of uterine enlargement and metastatic disease [8]. Lambrou *et al.* express a similar opinion that abdominal pain could be indicative of metastases within the abdomen [7].

Clearly, metastatic cancer, including endometrial cancer cannot be discounted in the event of a woman presenting with back, extremity, or hip pain. It is ironic that although 73.68% of cases presenting with bone pain are of stage 3 or 4 disease, and given that bone pain almost exclusively represents metastatic disease, that bone pain is associated with an almost 3 months longer time to diagnosis than is abdominal pain (mean time to diagnosis of 5.62 months and 2.71 months respectively). However, this may reflect a reporting bias favoring the reporting of difficult to diagnose cases presenting with bone pain, in lieu of cases in which the correct diagnosis of endometrial cancer was made more quickly. Of particular interest, 11 of 12 of the included cases previously treated with radiation for cervical cancer presented with abdominal pain 91.67%. Six of 12 cases (50%) of endometrial cancer following irradiation for cervical cancer were of advanced disease. Pothuri *et al.* found that 69% of cases of endometrial cancer following therapeutic irradiation for cervical cancer were of advanced disease [39]. Therefore, consideration for development of a second cancer should be given to persons with a prior history of cancer treated by radiation. Even if only 3.9 – 25% of women with endometrial cancer present with abdominal pain, the ten-fold difference in 5-year survival statistics for early and late stage disease supports a thorough evaluation.

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