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Endometrial Cancer Diagnosed by the Presence of Bone Metastasis and Treated with Zoledronic Acid: A Case Report and Review of the Literature

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Key Words

Bisphosphonates · Bone metastasis · Endometrial cancer

Abstract

Bone metastasis from endometrial cancer is rare. We report a case of endometrial cancer which was diagnosed by the presence of bone metastasis and treated with zoledronic acid. A 57-year-old woman complaining of progressive right hip pain consulted an orthopedist. She had no gynecologic complaints. X-rays revealed an osteolytic lesion of the right ischium. Bone scintigraphy was subsequently carried out and showed isotope accumulation in the right ischium. Computed tomography revealed an enlarged uterus; the patient consequently consulted a gynecologist. Histological sections of an endometrial biopsy showed endometrioid adenocarcinoma. Hysterectomy and bilateral salpingo-oophorectomy, as well as bone biopsy of the right ischium, were therefore carried out. A moderately differentiated endometrioid adenocarcinoma was expressed in the corpus. Histopathological examination of the bone biopsy also revealed adenocarcinoma. The final diagnosis was stage IVB endometrial cancer with bone and lung metastasis. Good pain relief was achieved due to chemotherapy. However, 2 months after completion of the chemotherapy, the patient was administered zoledronic acid because her hip pain had gradually increased. Following zoledronic acid administration, the hip pain reduced. Radiotherapy was then given for the right ischial metastasis after the ninth course of zoledronic acid therapy because the metastasis site had increased and the possibility of a pathological fracture had risen. However, the patient died 21 months after the initial treatment because of disease progression.

Introduction

Endometrial cancer is the most common malignancy of the female genital tract, and its incidence has increased remarkably. In Japan, the total number of endometrial cancer cases increased from 2,115 in 1994 to 4,267 in 2005 [1]. The first presenting symptom is commonly vaginal bleeding and most patients are at an early stage [2], resulting in a favorable overall survival rate. Endometrial cancer is more likely to metastasize to the lymph nodes, liver and lungs, while bone metastasis is very rare. Radiotherapy has been proven to play a palliative role in patients with bone metastases and administration of bisphosphonates, especially zoledronic acid, is used to prevent the symptoms of bone metastasis.

We report a case of endometrial cancer which was diagnosed by the presence of bone metastasis and treated with zoledronic acid, and review the related literature.

Case Report

A 57-year-old Japanese woman consulted an orthopedist, complaining of progressive right hip pain over a period of 2 months and lower abdominal pain. She had no gynecologic complaints such as vaginal bleeding. She was gravida 3, para 3, and menstruation had ceased at 44 years of age. Her medical history indicated that she had undergone a total gastrectomy, followed by chemotherapy, for treatment of gastric cancer 4 years previously. X-rays revealed an osteolytic lesion on the right ischium. Bone scintigraphy was carried out and showed isotope (technetium TC99m) accumulation in the right ischium and right pubis. These findings suggested that the lesion was likely to be a bone metastasis of the gastric cancer. However, computed tomography revealed an enlarged uterus with swelling of the para-aortic nodes and multiple lung nodes, which prompted a gynecologic consultation. Consequently, she was referred to our hospital for a gynecologic examination. Magnetic resonance imaging showed enlargement of the uterus, with a mass measuring 3 × 4 cm in the endometrial cavity. The mass showed heterogeneous medium and high signal intensity on T2-weighted images, and swelling of the left ovary was observed. An endometrial biopsy was performed and subjected to histological examination. Hematoxylin and eosin-stained sections showed a well-differentiated endometrioid adenocarcinoma. She was therefore diagnosed with endometrial cancer.

A hysterectomy, bilateral salpingo-oophorectomy and bone biopsy of the right ischium were carried out. Peritoneal cytology was negative. On pathological examination, a moderately differentiated endometrioid adenocarcinoma was expressed in the corpus and cervix of the uterus and left ovary. Histopathological examination of the bone biopsy revealed an adenocarcinoma that was CK7+/CK20- and ER+/PR+. The final diagnosis was stage IVB endometrial cancer with bone and lung metastases. The postoperative treatment consisted of paclitaxel (180 mg/m²) plus carboplatin (AUC = 6) for 6 cycles, because of the multiple metastases. As a result, good pain relief was achieved and the other metastases became smaller. However, 2 months after completion of the chemotherapy, the hip pain gradually increased, and she was administered zoledronic acid for symptom relief of the bone metastasis. After receiving zoledronic acid, her hip pain gradually reduced. Radiotherapy was given for the right ischial metastasis (37.5 Gy/15 Fr) after the ninth course of zoledronic acid therapy because the metastasis site had increased and the possibility of a pathological fracture had risen. However, the patient died 21 months after the initial treatment because of disease progression.

Discussion

Bone metastases are the most common malignant bone tumors, and their most common primary tumors are lung and breast cancers. Bone metastasis is rare in endometrial cancer, with a reported frequency of 0–8% [3, 4]. In an autopsy study, the corresponding frequency was 25–27% [5, 6] and the vertebrae were the most common

metastasis sites [5]. Bone metastasis is usually seen together with intra-abdominal and pelvic recurrences and/or other organ metastases. It is assumed that the mechanism of the vertebral metastasis involves Batson's paravertebral valveless venous plexus [7]. It is also possible that the vascular invasion could start in the lymphatics, where tumor cells gain access to the venous return and then to the systemic circulation via arterial outflow [8, 9].

The reported cases in the English literature obtained in searches of the PubMed and ScienceDirect electronic databases up to June 2010 are presented in [table 1](#) and [table 2](#). Table 1 shows the diagnostic cases of bone metastasis after initial treatment of endometrial cancer. In the 31 cases, the average interval between the detection of the endometrial cancer and the bone metastasis varied from 1 to 148 months (median, 17 months). A high incidence of bone metastasis with high-grade adenocarcinoma was revealed. All the patients complained of pain at the bone metastatic site, and the limbs and vertebrae were more frequently involved than the pelvis. Radiotherapy was frequently selected in the treatment of bone metastasis, and 18 patients died between 1 and 54 months (median, 8.5 months) after detection of the bone metastasis. Table 2 shows cases in which the bone metastasis was simultaneously detected at the time of the diagnosis of endometrial cancer. In those 21 cases, the most common first presenting symptom was pain and only 2 had vaginal bleeding. A high incidence of bone metastasis with high-grade adenocarcinoma was revealed, and showed the same pattern as the recurrence cases. Although the limbs were the most frequent metastatic sites, pelvic metastasis was more frequently observed in the initial diagnosis cases (33%) than in the recurrence cases (13%). This situation is considered to arise because the uterine tumors had stayed in the pelvis for a long time in the initial diagnosis cases. Radiotherapy was often selected in the treatment of bone metastasis. Ten patients died between 2 and 34 months (median, 9.5 months) after diagnosis. Although the first presenting symptom is usually vaginal bleeding and most patients are at an early stage of endometrial cancer, the first presenting symptom in these cases was hip pain, not vaginal bleeding. Therefore, there might have been a delay before the patients consulted a physician at the hospital.

In the present case, chemotherapy was chosen first because there were multiple distant metastases as well as the bone metastasis. As a result, the hip pain and tumor size were temporarily reduced. However, 2 months after completion of the chemotherapy, the hip pain had increased. The patient refused to receive further chemotherapy or hormone therapy. It has been reported that zoledronic acid may be effective for not only bone metastasis but also soft tissue organ metastases [10]. Therefore, only zoledronic acid was administered for pain relief. This case is the first report of administration of zoledronic acid for bone metastasis of endometrial cancer. Zoledronic acid was effective for the hip pain but could not suppress the growth of the bone metastasis. In this case, radiotherapy was not used concomitantly with zoledronic acid because of the multiple metastases. However, it has been reported that bisphosphonates seem to improve the clinical results obtained with radiotherapy in bone metastasis of renal cell carcinoma [11]. In our review, the median prognosis was 8–9 months' survival time after diagnosis of bone metastasis. Our patient survived for 21 months after detection of the bone metastasis, and zoledronic acid as well as chemotherapy and radiotherapy might have contributed to this outcome.

In conclusion, the present case involved bone metastasis from endometrial cancer, which is rare. Vaginal bleeding as the first symptom was absent, and consequently the disease was not detected until it had progressed to bone metastasis. In addition, this

report describes the use of zoledronic acid for bone metastasis of endometrial cancer for the first time.

Table 1. The diagnostic cases of bone metastasis after initial treatment of endometrial cancer (n = 31)

Case	Age years	Time to bone metas- tasis months	Histo- logy	Stage	Site(s) of bone metastasis	Other site(s) of metastasis	Symptom(s)	Treatment	Survival after bone metastasis months	Dead or alive
1	67	15	adeno	I	fibula		pain	RT	12	dead
2	59	9	G2	IC	femur	lung	pain, swelling	RT, chemo, HRT		
3	48	30	G2-G3	IIB	femur	lung	pain	RT, chemo, HRT	41	alive
4	77	24	G3	IC	metatarsus	lung	pain	amputation, RT, HRT	16	alive
5	86	18	SCC	IIIC	hallux	lung	pain	amputation		dead
6	67	4		IC	tibia, femur, metatarsus		pain	RT	2	dead
7	66	18	G3	IA	humerus		pain	RT, HRT	24	alive
8	45	36	G2	IA	cranium	lung	swelling	surgery, RT	6	dead
9	55	18	adeno		calcaneus, talus	lung	pain	RT	36	alive
10	55	24	G2	IB	calcaneus		pain	RT	10	alive
11	87	108			sternum		pain	surgery	60	alive
12	67	60	adeno	IVB	mandibula	lung, kidney	pain, swelling	surgery		dead
13	51	1	G3	IIIC	humerus	lymph node	pain	RT	6	alive
14	61		G1	IIIB	calcaneus		pain			
15	81	36	adeno	IIB	calcaneus		pain	RT		
16	70	24	G3	IC	ischium		pain	chemo, pamidronate	36	alive
17	61	44	G1	IIIA	vertebrae	any	pain	RT, surgery	12	dead
18	65	3	adeno	IIIB	vertebrae, rib	any	pain	chemo	9	dead
19	58	10	adeno	IA	L4, L5		pain	RT, surgery, chemo	199	alive
20	70	10	G3	IIB	vertebrae, rib, parietal	any	pain	RT	2	dead
21	65	7	G1	IIIB	tibia, femur	any	pain	RT, surgery	42	dead
22	55	25	adeno		pelvis, vertebrae, rib	any	pain	chemo	7	dead
23	60	12	clear		humerus, clavicle		pain	surgery, RT, chemo	13	dead
24	71	16	G2	IVB	L1, L3, L4	any	pain		1	dead
25	74	8	adeno	IB	vertebrae, rib	any	pain	RT, chemo	5	dead
26	62	11	G2	IIIC	calvarium, femur, spine	any	pain	surgery	54	dead
27	60	3	G3	IVB	sacroiliac joint	any	pain	RT, chemo	8	dead
28	52	148			vertebrae	any	pain	surgery	7	dead
29	55	9	G3	IIIC	rib, femur, spine		pain	RT, surgery	26	dead
30	40	3	G3	IIIC	ischium		pain	chemo	10	dead
31	56	26	G2	IC	femur	any	pain	surgery, chemo	12	alive

adeno = Adenocarcinoma; SSC = squamous cell carcinoma; RT = radiotherapy; HRT = hormone replacement therapy; chemo = chemotherapy.

Table 2. Cases of bone metastasis detected simultaneous with diagnosis of endometrial cancer (n = 21)

Case	Age years	Histology	Site(s) of bone metastasis	Other site(s) of metastasis	Symptom(s)	Treatment	Survival after bone metastasis months	Dead or alive
1	54	adeno	fibula		pain	RT, HRT, cordotomy	29	dead
2	61	G1	calcaneus, talus		pain, swelling	surgery, chemo, HRT	14	alive
3		G1	ischium		pain	RT	48	alive
4	71	G3	mandibula		bleeding	RT, chemo	14	alive
5	44	G2	femur		pain	surgery, RT, chemo	24	alive
6	59	G2	calcaneus		pain	RT, chemo, HRT	60	alive
7	73	G3	tibia		pain	chemo	9	dead
8	51	G3	cervical vertebra		bleeding	chemo	2	dead
9	70	G1	tibia		pain	RT, chemo	47	alive
10	64	CS	tibia		pain	RT	6	dead
11	39	G2	ischium		pain	surgery, RT	36	alive
12	63	G1	thoracic vertebra		unable to walk	surgery, RT	60	alive
13	76	G3	calcaneus		pain	chemo	19	dead
14	57		tibia	lung, kidney		RT		
15	67	G1	calcaneus, talus, metatarsal		pain	surgery	20	alive
16	55	G3	ischium, acetabulum, femur		pain	RT, surgery	10	dead
17	47	G2	vertebrae, acetabulum, femur, humerus		pain	chemo	7	dead
18	62	G3	vertebrae	any	pain	RT, chemo	16	dead
19	32	G3	pubic rami, acetabulum		pain	RT, chemo	5	alive
20	84	G2	ischium, superior ramus, acetabulum		pain	RT	34	dead
21	77	G3	inferior pubic ramus, sacrum, acetabulum	any	pain	RT, chemo	8	dead

adeno = Adenocarcinoma; RT = radiotherapy; HRT = hormone replacement therapy; chemo = chemotherapy.

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