Uterine endometrial carcinoma with DNA mismatch repair deficiency: Magnetic resonance imaging findings and clinical features

Abstract

Purpose:The purpose of this study was to identify the magnetic

resonance imaging(MRI) features of uterine endometrial

carcinoma(EC) with DNA mismatch repair(MMR) deficiency.

Materials and Methods:This was a retrospective study approved

by our institutional review board. The study included 118

patients pathologically diagnosed as having EC in our institution

from April 2014 to December 2016. Of 118 patients, 8 were

excluded because of insufficient data.Immunohistochemical

analysis of MMR was performed retrospectively to observe the

expressions of MLH1, MSH2, MSH6, and PMS2. A tumor with

MMR deficiency was detected in 17 of 110 cases (15%). Clinical

background characteristics and MRI findings were reviewed.

These findings were compared between MMR deficiency group

and the other group as a control group. Statistical significance

was determined <u>using the Fisher's exact test</u> and the Mann-Whitney U-test, as appropriate.

Results:The clinical background characteristics of patients with EC with MMR deficiency were not significantly different from those of other patients. On MRI, the tumor was significantly more often located in the lower uterine site (MMR(-) vs. MMR(+): 29.4% vs. 8.9% [p=0.0366]).

Conclusion:EC with MMR deficiency tends to be located lower in the uterus, though most other findings were not significantly different from those of EC without MMR deficiency.

Abbreviations

MMR: Mismatch repair

MSI: Microsatellite instability

ADC: Apparent diffusion coefficient

CRC: colorectal cancer

DWI: Diffusion-weighted imaging

IHC: Immunohistochemistry

MRI: Magnetic resonance imaging

TMA: Tissue microarray

EC: Endometrial carcinoma

T1WI: T1-weighted imaging

T2WI: T2-weighted imaging

CE-T1WI: Contrast-enhanced T1-weighted imaging

PTE: Peritumoral enhancement

SEE: Subendometrial enhancement

LUS: Lower uterine segment

MSI: Microsatellite instability

Introduction

The DNA mismatch repair gene (MMR) plays an important role in anti-carcinogenesis and MMR gene deficiency. Uterine endometrial carcinoma (EC) with MMR deficiency has been estimated to account for 23-35% of all cases of EC (1-3). Lynch syndrome, well known as hereditary non-polyposis colon cancer, is an autosomal dominant cancer caused by mutations of MMR genes (4-6). EC is the second most common malignancy associated with Lynch syndrome (2). However, the lifetime risk of EC in patients with Lynch syndrome is considered to surpass that of colorectal cancer (7-9). Recognizing EC with MMR gene deficiency may lead to early diagnosis of Lynch syndrome. To the best of our knowledge, the radiological findings of EC with MMR deficiency have not been previously reported, excepting for one article (10). The aim of this study was to identify the magnetic resonance imaging (MRI) features of EC with MMR deficiency.

Materials and Methods

Patients

This was a retrospective study approved by our

institutional review board. A total of 118 patients pathologically

diagnosed with EC in our institution from April 2014 to December

2016 were retrospectively identified. Of the 118 patients, 8 (6.8%)

were excluded because of no MRI data in this hospital.

On immunohistochemistry (IHC), 17 (14.4%) patients

(median age 54 years, age range 41-73 years) were pathologically

diagnosed as having EC with MMR deficiency. As controls in this

study, 93 (79.4%) patients (median age 56 years, age range 28-92

years) were pathologically diagnosed with EC without MMR

deficiency. Of the 93 patients, 3 did not undergo enhanced MRI

and diffusion-weighted imaging (DWI). In 5 of 93 patients,

dynamic MRI, DWI, and apparent diffusion coefficient (ADC)

values were invalid because the tumor was so small it could not be detected. In 15 of 93 patients, ADC values could not be used because of inappropriate data.

Of 17 patients, two did not undergo enhanced MRI, and one did not undergo DWI. In one of 17 patients, ADC values could not be used because of inappropriate data.

Patients' medical records were reviewed to check clinical background characteristics, including age, histopathological tumor grade, and the interval between MRI and surgery.

MRI technique

Since this was a retrospective review, MRI was performed using multiple systems. Sixty-one MRI examinations were performed in our institution using a 1.5-T MRI (MAGNETOM Avanto, Siemens, Forchheim, Germany) and 3-T MRI (MAGNETOM Verio, MAGNETOM Skyra, Siemens). Overall, 49 of 110 patients underwent MRI in other institutions. T2-weighted

imaging (T2WI) in 2 dimensions (axial and sagittal), fat-saturated

T1-weighted imaging (T1WI) with gadolinium contrast-enhanced

MRI, diffusion-weighted imaging (DWI), and ADC values were

reviewed. The details of the sequences are shown in Table 1.

Gadolinium-based contrast agents (Magnevist®, Gadvist®, Bayer

Healthcare, Osaka, Japan) were used for dynamic

contrast-enhanced (CE) MRI. Evaluable MRI sequences of this

study included T2WI, DWI, ADC values, and dynamic CE MRI.

DWI was performed with $b=1000$ sec/mm^2. Dynamic CE MRI was

obtained with the following parameters: injection speed 2 ml/s;

dose 0.1 mmol/kg; and scan timing (first and second phases) 60

and 120 s.

Imaging analysis

All images were retrospectively reviewed by 2 radiologists.

One was a radiologist with 5 years of experience, and the other

had more than 20 years of experience in genitourinary imaging. Consensus was reached by discussion.

The radiologists were blinded to clinical information and pathological/surgical findings of each patient. MRI was evaluated with respect to the following points: size, shape, location (corpus/isthmus/cervix), and site (upper site/lower site) of the uterine body, as well as intensity compared to normal endometrium on T2WI. DWI and ADC values (mean) could be evaluated in 90 and 85 patients, respectively. A total of 100 patients underwent dynamic contrast MRI studies so that the type of CE pattern and the presence of subendometrial enhancement (SEE) and peritumoral enhancement (PTE) were evaluated. SEE is the thin-layered enhancement between the endometrium and myometrium. PTE is recognized as focal strong or irregular enhancement around the tumor due to stromal reaction associated with myometrial invasion at the tumor front

(11). The SEE was evaluated in whole uterine cavity including the normal endometrial site and PTE was the linear enhancement located just between tumor and myometrium. The pattern of spread (expansile/infiltrated) and the presence of coexistent lesions (such as uterine leiomyoma) were also analyzed. Lesion sites were classified into two types: upper and lower. The upper site of the uterine body was defined as above the middle of the uterine corpus. The lower site of the uterine body was defined as below the middle of the uterine corpus (Fig. 1.). We classified to 3 groups following this definition. We defined upper site as the tumor volume occupied mainly uterine body to fundus, lower site as the tumor volume occupied mainly body to isthmus and cervix, and unknown as difficult to determine the tumor itself. So the four patients were excluded, as it was difficult for us to detect the tumor on MRI.

Pathological analysis

To observe the expressions of MMR proteins, tissue micro

arrays (TMAs) were constructed as follows. A small core was

punched from each formalin-fixed, paraffin-embedded tissue

block, and some cores were re-embedded into a TMA paraffin

block. The paraffin block was cut into 3-μm-thick sections using

a microtome, and a TMA slide was prepared. IHC staining for

TMA slides was performed using the monoclonal MLH1 antibody

(1:50; Clone ES05; Leica, Newcastle Upon Tyne, UK), MSH2

antibody (1:50; Clone 25D12; Leica), MSH6 antibody (1:100;

Clone PU29; Leica), PMS2 antibody (1:100; Clone M0R4G; Leica).

A trained pathologist (T.M.) blinded to the clinical information

evaluated the nuclear staining in the tumor cells. The expression

of DNA MMR proteins was defined as normal when nuclear

staining was seen in tumor cells. In others, loss of protein

expression was defined as absence of nuclear staining in tumor

cells, with intact nuclear expression in internal non-neoplastic tissues.

Statistical analysis

Statistical significance was determined using the Fisher's exact test and the Mann-Whitney *U*-test, as appropriate. The Mann-Whitney *U*-test was used to compare age, size, and ADC mean values. All statistical tests were conducted with a two-sided significance level of 5% using Prism 5 software (Graphpad Software Inc).

Results

Patients' clinical background characteristics

EC patients with MMR deficiency were slightly younger than those with MMR deficiency (median age: 54 vs 56 y [p=0.81]), though the difference was not significant. The interval between MRI and surgery was shorter for EC patients with MMR

deficiency than for those without MMR deficiency (mean=41.9±2.8 days vs. 44.1±2.9 days [p=0.7562]), but the difference was not significant.

The histopathological distributions (G1, G2 vs. others p=0.5793, G1 vs. others p=0.3056) also showed no significant differences between EC patients with and without MMR deficiency.

Of 17 EC patients with MMR deficiency, 13 (76.4%) were classified as FIGO I, 3 (17.6%) as FIGO III, and 1 (5.9%) as FIGO IV. On the other hand, of 93 EC patients without MMR deficiency, 75 (80.6%) were classified as FIGO I, 8 (8.6%) as FIGO II, 6 (6.5%) as FIGO III, and 4 (4.3%) as FIGO IV.

The results of IHC staining for MLH1, MSH2, PMS2, and MSH6 were: 9 patients showed loss of MLH1 and PMS2; 5 showed loss of MSH2 and MSH6; 2 showed loss of MSH6; and 1 showed loss of PMS2.

Imaging characteristics of EC with MMR deficiency

The MRI findings of EC with MMR deficiency are summarized in Table 2. The mean maximum diameter of the lesions was 42.5 mm (range 5.1-84.6 mm). 5 lesions (29%) were located in the fundus, 4 (23.5%) from the fundus to the corpus, 1 (5.8%) from the fundus to the upper corpus, 1 (5.8%) from the fundus to the cervix, 1 (5.8%) from the upper corpus to the cervix, 1 (5.8%) in the corpus, 1 (5.8%) in the middle corpus, 2 (11.7%) from the inferior corpus to the cervix, and 1 (5.8%) in the isthmus. Twelve (70.6%) lesions were located in the upper site of the uterus, with 4 (23.5%) in the lower site of the uterus and 1 (5.8%) in the isthmus.

In shape, 14 (82.3%) lesions were elevated-type, and 3 (17.7%) were flat elevated-type. We defined it as elevated type that tumor showed protruded mass or polypoid lesion clearly. And we defined it as flat elevated type that tumor showed slightly elevated flat

apperance to the endometrial cavity with or without myometrial invasion. This feature was reviewed retrospectively by 2 radiologists with consensus.

In the pattern of tumor spread, 12 (70.6%) lesions were expansile, with 4 (23.5%) infiltrated and 1 (5.8%) bulging.

On MRI, 17 lesions showed slightly high intensity on T2WI, and 1 (5.8%) showed heterogeneously high intensity; 16 lesions showed high intensity on DWI, and the mean ADC value was 0.597×10^{-3} (range 0.46-1.06×10^{-3}). In all 15 lesions, the dynamic CE pattern was the same (slight early enhancement and plateau). SEE was found in 4 (26.6%) lesions, and PTE was found in 8 (53.3%) lesions.

Pathological characteristics of EC with MMR deficiency

Six lesions of 17 patients (35.2%) were endometrioid carcinoma, grade 1, 5 (29.4%) lesions were grade 2, and 4 (23.5%) lesions

were grade 3; 1 (5.8%) lesion was large cell neuroendocrine cell tumor, and 1 (5.8%) lesion was mucinous differentiation-type.

Comparison between EC with and without MMR deficiency

A comparison between EC with MMR deficiency and the control group is summarized in Table 3. The most significant difference was noted in tumor site (upper site or lower site). EC with MMR deficiency was significantly more often located in the lower site [p=0.0366]. There was no significant difference in the tumor occurrence site in the isthmus (p=0.76) (Fig. 2).

EC with MMR deficiency was almost the same size as EC without MMR deficiency (mean 42.5±5.5 vs. 42.3±2.8 mm, p=0.97). The ADC value was slightly lower in EC with MMR deficiency than in EC without MMR deficiency (mean $0.65\pm0.05\times10^{-3}$ vs. $0.75\pm0,031^{-3}$, p=0.15). These parameters were not significantly different.

For the pattern of spread [>0.99], the shape [p=0.76], and the histopathological grade (G1, G2 vs. others p=0.58, G1 vs. others p=0.31), there were no significant differences between EC with and without MMR deficiency.

Discussion

MMR genes are responsible for the function of the DNA repair system during DNA replication and recombination, repairing mismatch of bases such as insertion, deletion, and misincorporation (12). Loss of the DNA MMR gene results in a strong mutator phenotype known as microsatellite instability (MSI), which is a hallmark of Lynch syndrome-associated cancer (13).

Lynch syndrome, an autosomal dominant inherited syndrome, is characterized by a high lifetime risk of multiple cancers such as

colorectal cancer (CRC), EC, and other organ cancers (2, 4, 14, 15).

Lynch syndrome retains heterozygous germline mutations in

MMR genes, encoding proteins such as MLH1, MSH2, MSH6, and

PMS2(16,17). Identification of patients with Lynch syndrome has

clinical significance because of the higher risk for synchronous or

metachronous malignancies in their lifetime(2). Moreover, in

patients with Lynch syndrome, the detection of EC is critical for

two reasons: one is that EC plays a role as the sentinel cancer,

and the other is that the lifetime risk of EC surpasses that of CRC

(7-9). Conventional screening for Lynch syndrome, such as the

Amsterdam II or revised Bethesda criteria, is predominantly

based on patient age (below 50 years old), family history, and/or

presence of Lynch-related tumor (2, 8, 18, 19). The efficacy of

these screening criteria is limited (1, 14, 20, 21).

IHC screening for MMR has attracted attention as a new

screening clue for Lynch syndrome (16, 19). Using this IHC

screening, staining for MLH1, MSH2, MSH6, and PMS2 could detect which MMR genes are deficient (8). However, some EC patients with MMR deficiency (35-60%) have no germline mutation in genes encoding MMR proteins (8, 22), and they are called Lynch-like syndrome or sporadic MMR deficiency (9, 14, 15, 23, 24). Recent data showed that first-degree relatives of patients with Lynch-like syndrome have an increased risk of CRC(22, 25). In the present study, EC with MMR deficiency accounted for 14.4% of all EC cases, lower than in previous reports from the United States (23-35%) (1-3). In Japan, it is still unclear exactly how many patients have EC with MMR deficiency, and racial differences could exist.

MRI features of EC in Lynch syndrome have been described in some papers (26-28). Though the specific MRI features remain unknown, some reports described the tumors as tending to locate in the lower uterine segment (LUS). These findings coincide with

Westin et al., who reported that 29% of carcinomas in LUS were associated with Lynch syndrome (29). They hypothesized that the reason for this tendency is that the microscopic appearance of glands and stroma in the LUS is different from the remainder of the endometrium, and LUS epithelium could be more susceptible to mismatch repair errors than that of the corpus (29, 30). MRI can show the mass of the EC and its location clearly. In the present study, the tumor locations of EC with MMR deficiency were significantly more common in the lower site of the uterine corpus than in EC without MMR deficiency. The high sensitivity of MRI for identifying the tumor location may be the key finding that leads to further screening for Lynch syndrome.

Though the location of EC depicted by MRI showed a significant difference, the other MRI findings, such as the size, the pattern of spread, the shape, and the enhancement pattern, were not significantly different between EC with and without MMR

deficiency.

Bhosale et al. reported that the ADC value on the reduced Field of View Diffusion Sequence could be a biomarker to identify EC with MSI caused by MMR deficiency that predisposed to mutation (10). MSI had been considered as having equivalent efficacy to IHC in predicting germline mutation (1,31). Thus, we also expected that the ADC value would be an effective radiologic parameter in differentiating EC with MMR deficiency. However, the ADC value also did not show a significant difference in the present study. We consider that the present result was reasonable because the histopathological grade of EC was not significantly different between EC with and without MMR deficiency. The histomorphologic differences between EC with and without MMR deficiency are still controversial (8, 32, 33). Further, the present results could be inconsistent with their result because both studies had small sample sizes, and their study enrolled patients

only with clinical FIGO stage 1 (10).

There were some limitations in the present study. The number of patients was small. In addition, cases of Lynch syndrome in patients having EC with MMR deficiency could not be confirmed by genetic screening. The additional genetic test was not agreed with the patients in this study. Two of 17 patients with MMR deficiency actually had other malignancy; one had the colorectal cancer, and the other the ovarian cancer, so that they are highly suspected as Lynch syndrome. The IHC staining was used to screen ECs with MMR deficiency that mainly consisted of Lynch syndrome with gene mutation. However, Lynch-like syndrome, which has a different germline gene mutation or somatic MMR mutation, and sporadic MMR deficiency could be intermingled. In fact, in the present study, 2 of 17 patients having EC with MMR deficiency also had colorectal cancer. Finally, the MRI images were retrospectively reviewed, so that the imaging technique

varied.

Conclusion

In this study, the MRI features of EC with and without MMR deficiency were compared. Though the MRI features of EC with MMR deficiency are nonspecific, the mass of EC with MMR gene deficiency tends to be located at a lower site of the uterine corpus, and this may be the key to stepping-up screening for Lynch syndrome.

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Figure legends

Fig. 1. T2WI sagittal image

The uterine corpus is divided into two equal sites: the upper site, being the upper half (a), and the lower site, being the lower half (b).

The endometrial carcinomas of the enrolled patients were assigned to the two groups depending on the main location of the tumor.

Fig. 2. A 53-year-old woman with EC with MMR deficiency

(a) T2WI (sagittal) shows circumferential endometrial thickening of the lower site of the uterine body spread to the uterine cervix. Hematometra is also seen (arrow).

(b,c) On contrast-enhanced T1-weighted imaging (axial), the mass shows slightly high intensity. Peritumoral enhancement is seen (arrow).

(d) MLH1, (e) MSH2, (f) MSH6, (g) PMS2 : IHC results are shown. Endometrial carcinoma shows loss of immunohistochemical expressions of both MSH2 and MSH6. Both MLH1 and PMS2 show normal expressions on IHC.

(h) HE stains show high-grade endometrial cancer (G3).

Table 1. Magnetic resonance imaging protocol

MR imaging parameter	T2-weighted TRA	SAG	T2-weighted imaging (3D)	T1-weighted imaging (2D)	T1-weighted imaging (3D)	DWI
Skyra/Verio						
Sequence	TSE	TSE	SPACE	TSE	VIBE	EPI
Respiration						
Flip Angle (degrees)	90	90	120/T2var	90	11	
TR	4500	4200	1600 /2700	500	4.38	9000/12100
TE	83	78	113/185	9.5	1.56	70 /78
FOV	200	230	250	200	250	300
Reduction factor	2	2	2	2	2	2
NEX	2	2	1.4	2	1	2/3
Thickness (mm)	3	3	1	3	0.9	4.5
Intersection gap (mm)	0.9	0.9	0	0.9	0	0

Avanto

Sequence	TSE	TSE	TSE	VIBE	EPI
Respiration					
Flip Angle (degrees)	90	90	90	12	
TR	3500	4000	519	6	4000
TE	83	76	8.7	2.19	70
FOV	200	250	200	250	320
Reduction factor	2	2	2	0	2
NEX	1	1	1	1	6
Thickness (mm)	3	3	3	1	7
Intersection gap (mm)	0.3	0.45	0.3	0	1.75

2D: two-dimensional, 3D: three-dimensional, TR: repetition time, TE: echo time, FOV: field of view

NEX: number of excitations, TSE: turbo spin echo, EPI: echo planar imaging, VIBE: volume interpolated breath-hold examination, SPACE: Sampling Perfection with Application optimized Contrast sing different flip angle Evolutions

Table 2.　Magnetic resonance imaging findings of EC with MMR deficiency

Case	Size (mm)	Shape	Location	Site	Pattern of spread	T2WI	DWI	ADC value	Early enhancement	DCE	PTE	SEE
Case 1	47	El	m.c	Lower	Ex	high	high	0.74	+	plateau	−	−
Case 2	30	El	c	Upper	Ex	high	high	0.70	+	plateau	+	−
Case 3	51	El	f-c	Upper	In	high	high	0.67	+	plateau	+	−
Case 4	45	El	f	Upper	In	high	high	0.61	+	plateau	+	+
Case 5	35	El	I	isthmus	Ex	high	high	0.62	+	plateau	+	−
Case 6	27	El	f-u.c	Upper	Ex	high	high	0.58	+	plateau	−	+
Case 7	85	Fl	f	Upper	In	high	high	0.53	+	plateau	−	−
Case 8	65	Fl	f	Upper	In	high	high	0.83	+	plateau	+	−
Case 9	77	El	f-ce	Lower	Bul	high	high	0.59		plateau		

Case 10	17	El	f	Upper	Ex	high	high		+	plateau	+	−
Case 11	59	El	f-c	Upper	Ex	high				plateau		
Case 12	61	Fl	i.c-ce	Lower	Ex	high	high	0.53	+	plateau	−	+
Case 13	15	El	f	Upper	Ex	high	high	1.06	+	plateau	−	−
Case 14	20	El	f	Upper	Ex	high	high	0.53	+	plateau	+	+
Case 15	5	El	f	Upper	Ex	high	high	0.46	+	plateau	−	−
Case 16	58	El	u.c-ce	Upper	Ex	high	high	0.73	+	plateau	+	−
Case 17	25	El	i.c-ce	Lower	Ex	high	high	0.47	+	plateau	−	−

El: elevated type, Fl: flat elevated type, u.c: upper corpus   m.c: middle corpus, i.c: inferior corpus, f: fundus, I: isthmus, ce: cervix

Ex: expansile pattern, I: infiltrative pattern, Bul: bulging pattern

Table 3. Comparison between EC with and without MMR deficiency

	Clinical background				MRI analysis			
	Age (y)	Histopathological grade	Size (mm)	ADC value	Pattern of spread	Shape	Tumor site containing isthmus	Tumor site
	(n=110)	(n=110)	(n=110)	(n=85)	(n=98)	(n=104)	(n=106)	(n=106)
		G1 vs others			Ex vs In	El vs Fl	Yes or No	L vs U
EC with MMR deficiency	54(41-73)	6 vs 11	42.5±5.563	0.6493±0.04608	12 vs 4	14 vs 3	5 vs 12	5 vs 12
EC without MMR deficiency	56(28-92)	46 vs 47	42.24±2.793	0.7514±0.03078	63 vs 19	68 vs 18	21 vs 68	8 vs 81
P-value	0.811	0.356	0.969	0.0148	>0.999	0.758	0.758	0.036*

MRI: magnetic resonance imaging, Ex: expansile, In: infiltrative, El: elevated type, Fl: flat elevated type, L: lower site of the uterus, U: upper site of the uterus