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A Layer of Decreased Apparent Diffusion Coefficient at the Endometrial-Myometrial Junction in Uterine Adenomyosis

Aki Kido[1*], Koji Fujimoto[1], Naoko Matsubara[1], Masako Kataoka[1],
Ikuo Konishi[2], and Kaori Togashi[1]

[1]*Department of Diagnostic Imaging and Nuclear Medicine, Graduate School of Medicine, Kyoto University,
54 Shogoin Kawahara-cho, Sakyo, Kyoto 606-8507, Japan*
[2]*Department of Gynecology and Obstetrics, Graduate School of Medicine, Kyoto University*

Objectives: To assess the detectability of a low-signal-intensity line within adenomyosis lesions adjacent to the endometrium on apparent diffusion coefficient (ADC) maps, and to establish correlations between these lesions and their possible causes, and more particularly the hormonal changes and magnetic resonance (MR) factors.

Materials and methods: MR images were obtained from 110 patients with adenomyosis (age 30–57 y.o.) using 3.0 T or 1.5 T MR units. Recognition of the low-signal-intensity line on ADC map was scored using confidence level. The correlation between recognition of the line and the following factors were examined: magnetic field strength, age group, menstrual cycle phases, history of delivery, and hormonal treatments. Presence of the structure corresponding to the low-signal-intensity line on ADC map was evaluated pathologically in the cases that underwent surgery.

Results: The low-signal-intensity line visible on ADC map was recognized in 55/110 patients. The visibility of the line was not significantly related to hormonal status, age, history of delivery, or magnetic resonance imaging (MRI) magnet strength. There were no corresponding pathological structures.

Conclusion: One half of the adenomyosis patients showed discrepant appearances in T_2-weighted (T_2WI) vs. ADC map, but no significant relationship with hormonal changes was found in this study. This result may suggest that the low-signal-intensity line within the junctional zone may be related to a functional phenomenon.

Keywords: *adenomyosis, apparent diffusion coefficient map, junctional zone*

Introduction

Adenomyosis is one of the common non-neoplastic diseases of the uterus. It is characterized by the presence of ectopic endometrial glands and stroma below the endometrial-myometrial junction (EMJ).[1,2] Pathologically, endometrial glands and stroma are typically surrounded by hyperplastic myometrium.[1] Therefore, on T_2-weighted (WI) images in magnetic resonance imaging (MRI), a diffuse or focal thickening of the junctional zone (JZ) with irregular margins can be observed, as well as a low-signal-intensity area in the inner myometrium.[3]

Recently, diffusion weighted imaging (DWI) has been widely used in body MR imaging. Because DWI enables visualization of the restricted diffusion of water molecules within the malignant tumors, it can be used for the detection of malignant lesions.[4] DWI provides quantitative measurements of apparent diffusion coefficient (ADC), which is a surrogate biomarker for the long or short outcome of a treatment.[4] In the ADC map of a normal uterus, the JZ is known to exhibit small structural changes according to the menstrual cycle.[5]

A number of reports have documented the morphology and pathophysiology of the uterine JZ.[6,7] Using pathological specimens, the decreased water content, nuclear area, and vascular density at the JZ were reported when compared to the outer myometriums.[6,8,9] Noe et al. reported a cyclic pattern of estrogen and progesterone receptor expression at the subendometrial myometrium.[10] However, no corresponding pathological structure has previously been described. By definition,

*Corresponding author, Phone: +81-75-751-3419, Fax: +81-75-771-9709, E-mail: akikido@kuhp.kyoto-u.ac.jp

the JZ structure cannot be distinguished from adenomyosis structures on T_2-WI simply because adenomyosis is described as a thickened layer of low signal intensity, similar to the JZ. In addition, it is also reported that the appearance of the JZ changes in function of the hormonal status.[11]

Recently we observed that, in patients presenting adenomyosis, a thin layer of restricted water diffusion may be visible at the EMJ on ADC maps. This structure looks very similar to JZ on T_2WI images (Fig. 1). However, this layer is not always visible in adenomyosis patients. We thus hypothesized that these differences may be due to various factors, which may lead to the changes in the appearance of the JZ.

The aim of this study was to investigate the detectability of this thin layer of restricted water diffusion within the adenomyosis lesions on ADC maps and to identify the possible causes such as magnetic field strength, patient age, hormonal status, and history of delivery. In several cases, histopathological specimens were also evaluated.

Materials and Methods

This retrospective study was approved by the Institutional Review Board of our institution.

In consecutive MRI studies of female pelvis, dating from October 2008 to October 2013, at our institute, we selected patients who were suspected to have adenomyosis, based on MRI findings. As an initial screening, past diagnostic reports for MRI containing the word "adenomyosis" were extracted from the reporting system in our radiology department. The original search yielded 180 studies. The patient cases were further selected using the following exclusion criteria: patients were excluded when (1) they were unable to evaluate the subendometrial myometrium in ADC map and (2) when malignancy was present within the uterine myometrium. Accordingly, 70 cases were excluded due to the following reasons: no DWI scanning (n = 2), difficulty in evaluating myometrial structure because of pregnancy (n = 6), multiple fibroids (n = 3), metal artifact (n = 2), and suspected malignancy within the uterine myometrium (n = 2). Thirty-four patients who presented a lesion of the adenomyosis located away from the endometrium were also excluded. Indeed, we evaluated patients developing adenomyosis which was in direct connection to the thickened JZ.[12] Seven patients presenting adenomyosis located at the uterine fundus, were also excluded since we evaluated ADC map using only the sagittal plane. In 14 patients, MR examination was carried out twice within that period. In those cases, the most recent MR examination was selected. In total, 110 patients were included in the study group, with age ranging from 30 to 57 years old

Fig. 1. Case of a 46-year-old woman with adenomyosis. Visualization score of the layer at the endometrial-myometrial junction (EMJ) is 4 (= definitely visible) in both readers. The patient has no history of pregnancy or hormonal intake. The image is obtained using a 3 T scanner. (**a**) T_2-weighted images show an enlarged uterus with thickened posterior wall and low signal intensity, characteristic of adenomyosis. (**b**) Diffusion weighted imaging with a b-value of 1000 sec/mm^2 shows homogenous signal intensity in the uterine myometrium. (**c**) Apparent diffusion coefficient map showing a thin layer of restricted water diffusion at the EMJ. This is seen not only at the anterior side but also at the site of adenomyosis.

(mean, 43.9 years). Of these 110 patients, 28 underwent surgery and were diagnosed with adenomyosis.

MR Scanning Protocols

MR examinations were performed using a 3.0 T MR (Skyra and Trio; Siemens Healthcare, Erlangen, Germany) and a 1.5 T MR unit (Avanto; Siemens

Healthcare, Erlangen, Germany) with a phased-array coil. Prior to MR examination, 20 mg of butylsco-polamine (Buscopan®; Nippon Boehringer Ingelheim Co. Ltd., Tokyo) was administered intramuscularly to reduce intestinal peristalsis, unless contraindicated or upon patient's refusal. At the beginning of the MR scan, coronal half-Fourier acquisition single-shot turbo spin-echo (HASTE) images [thickness = 3.0 mm with no gap, (repetition time/echo time) TR/TE = 1000/102 msec at 3.0 T, TR/TE = 1000/87 msec at 1.5 T] were obtained to provide an overview. Subsequently, sagittal fast spin-echo (FSE) T_2WI (thickness = 4 mm with a 1-mm intersection gap, TR/TE = 4500/83 msec, flip angle (FA) = 150° at 3 T, TR/TE = 5020/108 msec, FA = 150° at 1.5 T), sagittal spin-echo T_1WI (thickness = 4 mm with a 1-mm intersection gap, TR/TE = 608/11 msec, FA = 80° at 3 T, TR/TE = 594/11 msec, FA = 80° at 1.5 T), axial FSE T_2WI (thickness = 4 mm with a 1-mm intersection gap, TR/TE = 4500/81 msec, FA = 150° at 3 T, TR/TE = 4960/105 msec, FA = 150° at 1.5 T) were performed. All sagittal images including those following DWI were obtained with a 4-mm thickness and a 1-mm intersection gap. Sagittal DWI were obtained in the same plane as T_1WI and T_2WI using a single-shot echo-planar (EPI) sequence (TR/TE = 4800/75 msec at 3 T, TR/TE = 3000/70 msec at 1.5 T; motion-probing gradients in three directions with b factors of 0, 100, 500, 1000 sec/mm^2) with spectral adiabatic inversion recovery (SPAIR) at 3.0 T and chemical shift selective (CHESS) at 1.5 T for fat suppression. Following acquisition, contrast enhancement was performed with intravenous administration of gadolinium contrast agent in 15 patients. Contrast-enhanced sagittal and axial SE T_1WI images (T_1WI, TR/TE = 600/9.3 msec, FA = 120° at 3 T, TR/TE = 450/17 msec, FA = 90° at 1.5 T) were acquired. Five patients underwent a dynamic contrast-enhanced MRI (DCE-MRI) in the sagittal plane (TR/TE = 608/11 ms, slice thickness 4 mm; intersection gap 1 mm). These sequenced images were acquired at different times (20, 40, 60, 80, 100, 120, and 180 s) following injection of the contrast agent (0.2 mL/kg of gadoterate dimeglumine at a flow rate of 2 mL/s).

Evaluation of MR Imaging Findings

The thin layer of restricted water diffusion adjacent to the endometrium, as recognized on ADC map, was scored as follows: score 1 = not visible, score 2 = undetermined, score 3 = probably present, score 4 = definitely visible. Two radiologists with, respectively, 5 years and 17 years of experience in female pelvic MRI, examined the findings independently. When the outcomes differed, agreement was reached by consensus.

In order to investigate the existence of a potential correlation between the scores assigned upon visual evaluation, the influence of magnetic field strength and patient background were examined: (1) magnetic field strength (3 T vs. 1.5 T), (2) age ranges (30–34, 35–39, 40–44, 45–49, 50–54, and 55–59 y.o.), (3) menstrual cycle phases (menstrual, follicular, and luteal phase), (4) history of delivery (parous vs. nulliparous), and (5) use of hormonal agent or oral contraceptives within 2 months of the MRI scan. The menstrual cycle phase was estimated based on the last menstrual day and the duration of the menstrual period, as recorded in the medical archives.

In patients who underwent a dynamic study, the presence of subendometrial enhancement (SEE) was evaluated by two radiologists with consensus. SEE occurs when the thin layer forming between the endometrium and the myometrium is slightly enhanced (initially) on dynamic MR images.[13]

In patients who underwent surgery, the presence of a corresponding structure on ADC map was checked pathologically.

Statistical Analysis

Statistical analyses were performed using MedCalc® version 12.3.0, MedCalc Software, Ostend, Belgium). Concordance of visual scores between the two readers was evaluated by weighted kappa coefficient. Comparison between the visualization score vs. MRI field strength, reproductive history and use of hormonal agent/oral contraceptive, was carried out using the Mann-Whitney U test. The Kruskal-Wallis test was used for comparison between the visualization score vs. age and vs. menstrual cycle.

Results

Visual evaluation allowed rating the patient cases between 1 and 4. In total, 41, 14, 23, and 31 cases, were assigned the scores 1, 2, 3, and 4, respectively. The concordance between the two readers was 0.65, meaning that there was a good agreement (Figs. 1, 3).

In Table 1, the relationship between visualization score and magnetic field strength is summarized. Seventy-six cases underwent MRI scans at 3 T unit (Skyra and Trio) and 34 cases at 1.5 T unit (Avanto). There was no significant difference between the 1.5 T and the 3 T group ($P = 0.132$).

To assess a possible correlation with age, the cases were divided into six groups using 5-year intervals; i.e., 30–34, 35–39, 40–44, 45–59, 50–54, and 55–60 years old. The score distribution within each group is summarized in Table 2. There was no significant difference among the groups ($P = 0.242$).

Confirmation of the menstrual cycle phase was possible in 51 out of 110 cases. In Table 3, the scores for

Fig. 2. Case of a 42-year-old woman with adenomyosis. The visualization score of the layer at the endometrial-myometrial junction (EMJ) is equal to 1 (i.e., not visible) by both readers. The patient has a history of pregnancy but no history of hormonal intake. The image is obtained at 1.5 T scanner. The patient's menstrual cycle is irregular. (**a**) T_2-weighted shows diffuse adenomyosis of the uterus. Small high signal spots are observed in the endometrial tissue. (**b**) Diffusion weighted imaging with a b-value of 1000 sec/mm^2 shows heterogeneously low signal intensity of the uterine myometrium. (**c**) On apparent diffusion coefficient map, layer-like structure at the EMJ is not visible.

each cycle are summarized. There was statistically no significant difference ($P = 0.062$).

In Table 4, the scores in function of the reproductive history are represented. In five cases, the history of delivery was unknown. No significant difference was determined ($P = 0.433$).

In Table 5, the visualization scores in function of hormonal intake are indicated. A total of 26 patients were undergoing treatment with hormonal agent (GnRH

Fig. 3. Case of a 51-year-old woman with adenomyosis. Visualization score of the layer at the endometrial-myometrial junction (EMJ) is 3 (= probably present) and 4 (= definitely visible) by two readers. The patient has a history of pregnancy but no history of hormonal intake. The image is obtained at 3 T scanner at the luteal phase. (**a**) T_2-weighted (WI) shows an enlarged uterus with several fibroids and a thickened posterior wall with adenomyosis. (**b**) On dynamic contrast enhancement T_1WI, subendometrial enhancement is observed all around the subendometrium. (**c**) Diffusion weighted imaging with a b-value of 1000 sec/mm^2 shows low signal intensity of the posterior uterine myometrium with slightly high signal intensity in fibroid in anterior wall. (**d**) Apparent diffusion coefficient map showing a layer of restricted water diffusion both in the posterior wall (the site of adenomyosis) and in the anterior wall of the uterus. This layer is not clearly visible at the site of submucosal fibroid.

Table 1. Comparison between the magnetic field strength of the scanner and the scores of the layer with decreased water diffusion at the endometrial-myometrial junction on apparent diffusion coefficient map. There was no significant difference between the two groups (Mann-Whitney U test, $P = 0.132$)

Magnetic field strength	Score 1	Score 2	Score 3	Score 4	Total
3 T	32	7	16	21	76
1.5 T	9	7	7	11	34
Total	41	14	23	32	110

Table 2. Comparison between age groups and scores of the layer with decreased water diffusion at the endometrial-myometrial junction on apparent diffusion coefficient map. There was no significant difference among the groups (Kruskal-Wallis test, $P = 0.242$)

Age group	Score 1	Score 2	Score 3	Score 4	Total
30–34	3	1	0	1	5
35–39	7	1	6	5	19
40–44	13	4	4	9	30
45–49	10	6	10	14	40
50–54	5	1	3	3	12
55–59	3	1	0	0	4
Total	41	14	23	32	110

Table 3. Comparison between menstrual cycle changes and scores of the layer with decreased water diffusion at the endometrial-myometrial junction on apparent diffusion coefficient C map. There was no significant difference between two groups (Kruskal-Wallis test, $P = 0.062$)

	Score 1	Score 2	Score 3	Score 4	Total
Menstrual phase	2	1	1	5	9
Follicular phase	3	2	5	3	13
Luteal phase	16	1	6	6	29
Unknown					59
					110

Table 4. Comparison between reproductive history and scores of the layer with decreased water diffusion at the endometrial-myometrial junction on apparent diffusion coefficient map. There was no significant difference between two groups (Mann-Whitney U test, $P = 0.433$)

Reproductive history	Score 1	Score 2	Score 3	Score 4	Total
(+)	18	8	14	16	56
(−)	22	4	9	14	49
Unknown					5
Total	40	12	23	30	110

Table 5. Comparison between hormonal intake and scores of the layer with decreased water diffusion at the endometrial-myometrial junction on ADC map. There was no significant difference between any two groups (Mann-Whitney U test, $P = 0.408$)

Hormonal intake	Score 1	Score 2	Score 3	Score 4	
(−)	29	11	20	24	84
(+)	12	3	3	8	26
Total	41	14	23	32	110

Table 6. The presence of SEE and the visualization score of each patient

Case	Score	SEE
1	4	(−)
2	4	(+)
3	3	(+)
4	1	(+)
5	1	(−)

SEE, subendometrial enhancement.

analogue, progestational agent) or oral contraceptive. One patient was in puerperal period and one patient in menopausal. No significant difference was determined ($P = 0.408$).

Five patients underwent a dynamic study. The results are summarized in Table 6 (Fig. 3).

Of the 28 patients who underwent surgery, the layer of restricted water diffusion was visible in eight of the patients. In those eight patients, uterine adenomyosis was pathologically recognized at the same part with MR imaging. However, no corresponding structures were recognized in any of the pathological specimens both in area with and without adenomyosis.

Discussion

The results showed a discrepancy in the appearance of T_2WI vs. DWI/ADC in nearly half of the patients diagnosed with adenomyosis. We hypothesized that the visibility of the layer of restricted water diffusion is related to hormonal status, age, history of delivery, and magnet strength; however, a significant correlation was not established.

Because the uterine myometrium showed dynamic changes in the T_2WI of MRI in function of hormonal status, it was expected that the appearance of the layer at the EMJ in ADC map might also vary in the function of hormonal status.[14,15] Our results showed that menstrual cycle and hormonal therapy were not significantly

correlated with the recognition of low-signal-intensity lines. The most drastic change in hormonal status may occur during the menopause. However, the cohort included only one menopausal patient, thus we were not able to visualize adenomyosis on ADC map in pre- vs. post-menopausal subjects. These investigations will be carried out in the next stage.

DW images at 3 T are known to exhibit higher signal-to-noise ratio and higher resolution without the introduction of noise-related errors, regardless of the increased geometric distortions caused by 3 T magnetic field inhomogeneity.[16] On the other hand, increased susceptibility is another characteristic of 3 T MRI. Since this structure of low-signal-intensity line has not previously been reported, we expected that this structure would be better visualized at 3 T. However, there was no difference in recognition between 1.5 T and 3 T. Because the structure consists of a thin layer, high special resolution imaging of DWI using readout-segmented echo-planar imaging might result in improved conspicuity.[17–19]

During pregnancy, a remarkable uterine growth is induced due to smooth muscle hypertrophy.[20] During this period, the inner wall of the uterine body contains more muscle than the outer layers.[20] Subendometrial low-signal-intensity layer was not affected by this prominent structural change of the uterus. This suggests that the low-signal-intensity layer is not affected by structural changes. Since we did not examine any case of pregnancy, further investigation is required to assess this possibility.

The presence of a layer visible only in ADC map suggests that there is an area of restricted diffusion that was not detectable on T_2WI. Pathologically, adenomyosis is characterized by the presence of endometrial glands within the myometrium and often accompanies a smooth muscle hyperplasia with a diffusely thickened, trabeculated myometrium.[1,21] Given the microscopic muscular changes in adenomyosis, one would expect changes, to some extent, in the layer of restricted water diffusion. Our observations revealed, however, that this layer was preserved in nearly half of the patients. Since we were not able to identify any corresponding structure in pathologic specimens, we suggest that the layer visible in ADC map reflects a functional structure visible only *in vivo*, rather than an anatomical structure.

Functional aspect of JZ has previously been suggested by Lee et al. on the basis of radiologic-pathologic correlation of the uterus *ex vivo*.[7] We would consider the possible relation with uterine peristalsis as a functional phenomenon of this low-signal-intensity line, as suggested by Nakai et al.[22] Uterine peristalsis is usually depicted as a low-signal-intensity conduction within the JZ.[22–25] Quantitatively, this movement is reflected as a change in JZ thickness and signal intensity.[26] If a low-signal-intensity line within the adenomyosis

reflects this subtle contraction, restricted diffusion in this area could be explained. However, there is a conflict with the feature of uterine peristalsis of strong relation with menstrual cycle phase and hormonal condition.[24,27] From these facts, the low-signal-intensity conduction may not directly display the subtle contractions of the subendometrial myometrium, but may demonstrate several complex causes, such as perfusion, contraction, and so on.

Dynamic contrast-enhanced study was carried out in five of the patients. Although the appearance of SEE was similar to the line visible on ADC map, the presence of SEE corresponds to the visibility of low-signal-intensity line on ADC map in three out of five patients. The early and strong enhancement of the subendometrium may be related to the abundant vascular density present in the JZ compared to the outer myometrium.[28] If the low-signal-intensity line is related to a functional phenomenon, the vascularity within the myometrium may also relate to the structure. Larger patient cohort will be required to examine these potential relationships.

There were several limitations in this study. First, we did not evaluate the ADC map of a normal uterus. A larger cohort of healthy volunteers (control) is required to further discuss the MR findings presented in this report. Second, comparisons of pre- vs. post-menopausal patients as well as pre- vs. post-hormonal therapy, which correspond to the most prominent changes in hormonal status, were not performed due to the limited number of subjects. Third, a detailed examination of the pathological specimen, e.g., investigation of nuclear area, vascular density, and hormonal receptor, was not conducted in this study. Further investigations are required to identify the corresponding structures in pathological specimens. Finally, we were not able to correlate early enhancement at the EMJ due to the limited number of subjects.

In conclusion, a thin layer of restricted water diffusion was seen in nearly half of the patients diagnosed with adenomyosis. The formation of this layer was not significantly related to hormonal status, age, history of delivery, and the magnetic field strength of the scanner. Further investigations are required to identify the physical, physiological, or pathological background that will explain the differences observed.

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