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Title

MR imaging manifestations of decidualized endometriotic cysts: Comparative study with ovarian cancers associated with endometriotic cysts.

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Abstract

Purpose. To investigate the MR findings of decidualized endometriotic cysts in comparison with endometriotic cysts associated with ovarian cancers.

Methods. Eighteen decidualized endometriotic cysts and 24 ovarian cancers were retrospectively assessed on height, signal intensity of the solid component on T2- and DWI, ADC value of the solid component, size of the lesion, and signal intensity of the intracystic fluid on T1-WI.

Results. The heights of the solid components in decidualized endometriotic cysts were inferior to 11.1mm, significantly lower compared to ovarian cancers. Similarly, decidualized tissues showed significantly higher signals on T2-WI and higher ADC values compared to ovarian cancers, but not on DWI. Decidualized endometriotic cysts were also significantly smaller. Intracystic fluids showed higher signal in decidualized endometriotic cysts compared to ovarian cancers on T1-WI.

Conclusion. In pregnant subjects, the presence of endometriotic cysts with low-height solid component showing high signal intensities on T2-WI is highly indicative of decidualization.

Keywords: endometriotic cyst, decidual change, placenta, pregnancy, MRI

Introduction

Endometriosis is a disease commonly affecting the reproductive woman. Although the reported prevalence of the disease varies from 1%-7% to 10-15%, its incidence increases with age up until the mid-forties[1]. Recently, the maternal age at pregnancy has increased owing to progress in the treatment of infertility. As such, the prevalence of gestation in patients with endometriotic cyst is expected to be on the rise.

Decidualization of the ectopic endometrial tissue, including the endometriotic cyst, is known to occur during pregnancy[2]. This is a transient condition associated with high serum level of progesterone, and when the ectopic decidua undergoes hyalinization in postpartum patients[3], it then disappears or shrinks. In order to reduce unnecessary and extensive examinations on the patient and the fetus, it is critical to be able to distinguish such non-neoplastic condition from malignant lesions. The appearances of an ectopic decidualization and that of a malignant transformation are very similar on both ultrasonography (US) and MRI. US allows an early detection of the lesion within the ovarian endometriotic cysts. However, an accurate diagnosis becomes more challenging to establish when the solid component is detected, because rapid growth and abundant vascularization on US are commonly seen in decidualized tissue as well as in malignancy[4, 5].

Magnetic Resonance (MR) imaging may represent a key tool to address the problem; it is a minimally-invasive technique when performed after the first trimester[6], and provides a high contrast visualization of the tissue and/or the lesion. Of the reports documenting the appearance of decidualized endometriotic cysts in MR imaging, Tanaka *et al.* described that the excrescence resulting from the decidualized endometriotic cyst exhibited an intensity similar to that of the placenta on T1- and T2-weighted images[7]. Takeuchi *et al.* reported the apparent diffusion coefficient (ADC) values calculated from diffusion-weighted images obtained from differentiating malignant ovarian tumors[8]. However, there has been no previous report on the quantitative analysis of signal intensities, nor on the morphological analysis of MR images.

Thus, the purpose of our study is to investigate the MR findings of decidualized endometriotic cysts both morphologically and on the basis of signal intensities, in comparison with ovarian cancers associated with endometriotic cysts.

Materials and Methods

The protocol used in this retrospective study was approved by the Institutional Review Board of our institution. Written informed consent was obtained from all participants.

In a serial 7080 MRI study starting from May 2002 to November 2011 and involving the examination of female pelvis at the Kyoto University Hospital, 14 patient cases were suspected to exhibit decidualized endometriotic cysts upon MR examinations. Of these 14 cases, two were histopathologically confirmed as decidualized endometriotic cyst by surgical resection during pregnancy, while the others were clinically diagnosed by detection of the intracystic solid component and their shrinkage or disappearance on periodical TVUS and/or MR imaging. The age of the patients ranged from 17-36 years (average of 31 years), and the gestational age on the first MR exam in our hospital ranged from 9-19 weeks (average 14.1 weeks). Detailed clinical information of patients with decidualized endometriotic cysts is provided in Table 1.

Bilateral lesions were considered as two separate lesions. Since bilateral lesions were detected in four cases, a total of 18 lesions of decidualized endometriotic cysts were evaluated. Diffusion-weighted images (DWI) were available in 12 lesions originating from 10 distinct patients.

A comparative analysis was performed against 20 patient cases of ovarian carcinomas associated with endometrial cysts. These cases were selected from serial 4614 studies diagnosed between November 2005 and July 2011 at the Kyoto University Hospital. Among them, eleven clear cell carcinomas and nine endometrioid adenocarcinomas were included. All these patients underwent surgical resection of the lesions, which were histopathologically confirmed as ovarian carcinomas with a suspected association with endometriotic cysts. The patients ranged between 43 and 68 years (average of 54 years) of age. Bilateral lesions were detected in four cases, thus a total of 24 lesions of ovarian carcinomas associated with endometriotic cysts were evaluated.

MR scanning protocols

MR scans were performed utilizing a 1.5T unit (Magnetom Symphony or Avanto; Siemens Medical System, Erlagen, Germany) with a six-channel phased-array coil. In both patients with decidualized endometriotic cysts and those with ovarian carcinomas, axial and sagittal fast spin-echo (FSE) T2-weighted images, spin-echo (SE) T1-weighted images and DWI were obtained for image analysis. Sagittal T1-weighted images with fat-suppression were utilized for the precise diagnosis of intracystic

hemorrhage in all patients. Contrast-enhanced T1-weighted images were utilized for the clinical diagnosis of patients with malignancy upon administration of the gadolinium-contrast agent Magnevist® (Bayer Yakuhin Ltd., Osaka, Japan) at a dose of 0.2 mmol/kg intravenously. The anti-cholinergic drug Buscopan® (Nippon Boehringer Ingerheim Co., Ltd., Tokyo, Japan) was used as pre-medication for the suppression of motion artifacts caused by bowel peristalsis in all patients with ovarian carcinoma, except in two cases, one patient was exhibiting cardiac disorders and the other patient disapproved. None of the contrast material or pre-medication drugs were utilized in pregnant patients.

Detailed scanning protocols and parameters were as follows: Axial FSE T2-weighted images: TR/TE = 4000/100-120 msec; flip angle (FA) = 150; ETL= 15; bandwidth = 140 Hz/pixel; matrix size = 512 × 348; slice thickness=5mm with 1.5mm gap, sagittal FSE T2-weighted images: TR/TE = 4000/100-120 msec; FA = 150; ETL= 15; bandwidth = 140 Hz/pixel; matrix size = 512 × 348, sagittal SE T1-weighted images: TR/TE = 500 /11 msec, FA = 80, ETL=1; bandwidth=130 Hz/pixel; matrix size = 512 × 348. The chemical shift selective (CHESS) technique was used for fat-suppressed spin-echo sagittal T1-weighted images.

After acquisition, DWI were obtained in the same sagittal plane as T1- and T2-weighted images using a single-shot echo-planar imaging (EPI) sequence (TR/TE= 3000/72 msec, FA = 90/180, number of averages = 3, bandwidth = 1700 Hz/pixel; matrix size=128*81; motion-probing gradients (MPGs) in three directions with b-factors of 0, 500 and 1000 sec/mm^2) with CHESS for fat suppression. All sagittal images including DWI were obtained with a 5mm-slice thickness =, an intersection gap of 1.5 mm. ADC maps were automatically calculated on a pixel-by-pixel basis from the DWI for quantitative analysis.

T1- and T2-weighted images were obtained in all patients with decidualized endometriotic cysts, but DW images were available for only 12 lesions out of 10 cases because DWIs are not routinely scanned at our institute when subjects are pregnant. In all 20 patients with ovarian carcinomas, all sequences described above were scanned.

While the same protocol and equipment were used to scan both pregnant patients and ovarian cancer patients, adjustments were made to take into account the limitation of specific absorption rate (SAR) or the size (gestational age) of the patients.

Image Analysis

One experienced radiologist (BLIND, 13 years of experience in gynecological radiology) measured the following parameters using axial and sagittal T2-weighted

images: (1) height of the intracystic solid component from the cyst wall or the septum, and (2) maximum diameter of the entire lesion including both solid and cystic components. T1-weighted images were utilized as reference.

Two experienced radiologists (BLIND and BLIND, 13 and 17 years of experience, respectively) measured the signal intensity (SI) of the following objects in conference manner using a commercially available software (Centricity®, GE Healthcare Japan, Tokyo, Japan). Bilateral lesions were considered as separate lesions. When more than one lesion per ovary was observed, only the largest lesion was evaluated.

The SIs of intracystic solid components and iliopsoas muscles were measured on T2-weighted images and DWI with a b-value of 1000 sec/mm^2 (DWI_{1000}). The SI of the placenta was also measured in the pregnant subjects. The regions of interest (ROIs) in oval shapes of all measurements were placed as large as possible with reference to T2-weighted images and DW images with a b-value of 500 sec/mm^2, avoiding areas with artifacts caused by air interface or blood flow.

The signal intensity ratio between the solid components and the muscles (SIR_solid) was calculated using the following equation: SIR_solid = (SI_solid – SI_muscle) / SI_muscle.

The signal intensity ratio between the placenta and the muscle (SIR_placenta) was calculated using the following equation: SIR_placenta = (SI_placenta – SI_muscle) / SI_muscle.

The signal intensity of the intracystic fluid and iliopsoas muscle were measured on T1-weighted images. The ROIs of the intracystic fluid component on T1-weighted images were placed as large as possible in the cysts avoiding areas with artifacts. The ROIs on the iliopsoas muscle and the placenta were carefully placed at the center of the object, again to minimize artifacts. The signal intensity ratio between the intracystic fluid and the iliopsoas muscle (SIR_fluid) was calculated as follows: SIR_fluid = (SI_fluid – SI_muscle) / SI_muscle.

The ADC values of the intracystic solid components and those of the placenta were measured in pregnant subjects using an automatically-calculated ADC map. The ADC values of the solid components and the placentas were measured using the same ROIs as the values used for measuring SI.

Statistical analysis

An unpaired t-test was used to compare values between lesions of decidualized endometriotic cyst (decidua group) and those of ovarian carcinomas (cancer group): height of the intracystic solid component between the lesions, SIR_fluid on

T1-weighted images, SIR_solid on T2-weighted images, SIR_solid on DWI_{1000} and ADC values. Difference between SIR_solid of decidua group and SIR_placenta on T2-weighted images and DWI1000. Differences between the ADC values of the solid component in the decidua group and the placenta were evaluated using paired t-test. A p-value of less than 0.05 was considered significant difference. All statistical analyses were conducted with StatView® software package (Version 5.0, SAS Institute Inc. Cary, NC, USA).

Results

All 18 lesions of decidualized endometriotic cysts and 20 cases of ovarian carcinomas were visualized with sufficient image quality to allow for both qualitative and quantitative evaluations. In all 18 lesions, the heights of the intracystic solid components, as measured from the cystic wall or the septum were inferior to 11mm and there was no overlapping value with the cysts found in carcinomas (Fig. 1). Representative cases are shown in Figures 2 and 3. Other results are also summarized in Table 2. In the decidua group, the mean and standard deviation (SD) of the height of the intracystic solid component was 7.7 ± 1.5mm, while that in the cancer group was 28.5 ± 12.5mm. The maximum diameter of the entire lesion (mean ± SD) in the decidua group and the cancer group were 60.0 ± 23.3 mm and 124.5 ± 56.8mm, respectively (Table 2). Both the diameter of the entire lesion and the height of the intracystic solid component were smaller in the decidua group compared to the cancer group, with statistical significance ($p<0.0001$).

On T2-weighted images, the SIRs of the intracystic solid component (mean ± SD) in the decidua group, the cancer group and the placentas were 11.6 ± 4.5, 3.7 ± 1.0 and 8.9 ± 2.6, respectively (Table 2). The SIR of the decidua group was significantly higher than that of the cancer group ($p < 0.0001$) and similarly for the placenta ($p = 0.03$).

On DWI_{1000}, the SIRs of intracystic solid component (mean ± SD) in 12 lesions of the decidua group, the cancer group and the placentas were 2.0 ± 0.6, 2.5 ± 0.9 and 2.2 ± 0.6, respectively (Table 2). On DWI_{1000}, the SIR_solid of the decidua group was relatively lower than that of the cancer group, but not statistically significant ($p = 0.09$). Differences between the decidua group and the placenta were also not statistically significant ($p = 0.52$).

The ADC values of the intracystic solid component in the decidua group, that in the cancer group and the placentas were 1.77 ± 0.27($10^{-3}mm^2$/sec), 1.13 ± 0.24 and 1.72 ± 0.36, respectively, and the solid component of the decidua group showed

significantly higher value than that of the cancer group ($p < 0.0001$) (Table 2). No statistically significant difference was observed between the decidua group and the placenta ($p = 0.48$).

On T1-weighted images, the SIRs of the intracystic fluid (mean ± SD) in the decidua group and the cancer group were 3.3 ± 2.3 and 0.9 ± 1.0, respectively (Table 3). The SIR of the intracystic fluid in the decidua group was significantly higher than that in the cancer group ($p = 0.0001$).

Discussion

In our study, all decidualized components on the wall of the endometriotic cyst were observed as low-growing component along the cystic wall or the intracystic septa, about 1cm below. Even when the decidualized component was seen as an apparent massive form in images of one cross-section, it actually formed a thin broad structure. The appearance of the decidualized endometriotic cyst described above might be helpful for their distinction from the malignant transformation of the endometriotic cyst. Similar MR appearances have been described previously. Takeuchi, *et al.* described that most of the mural nodules were small and inferior to 1cm of size, except for one lesion[8]. Similar appearance on MR imaging can be inferred from most other case-reports[7, 9-13].

The low-growing structure of the solid component within the decidualized endometriotic cyst might be explained by its histopathogenesis. Ectopic endometrial tissue on the cystic wall can include endometrial stromal cells, which have the potency to turn into decidual cells. Decidualization of the endometriotic cyst is distinct from a neoplastic change, as it only represents a response of the indigenous stromal cells of the cystic wall to the hormonal changes occurring during pregnancy[3], similarly to the changes taking place in the uterine endometrium. In the fertile uterus, “normal” decidualization of endometrial stromal cells results in a thin broad sheet of decidual membrane covering the chorionic tissue. If a similar change occurs on the wall of the endometriotic cyst, it is likely that the decidualized tissue will form a low-growing structure. As the form of the decidualized tissue is affected by the amount of endometrial stromal cells within the wall and the degree of hormonal variation, it is not expected to form the tall mass characteristics of carcinomas, which grows autonomously.

The maximal diameter of the cyst was also significantly smaller than that observed in ovarian cancers. Previously and in line with our results, Tanaka *et al.* reported that endometriotic cysts associated with ovarian carcinomas exhibited significantly larger cysts compared to benign endometriotic cysts[14, 15].

Another interesting feature of the decidualized endometriotic cysts examined in the present study is the high signal intensity of its solid component on T2-weighted images. The solid components of decidualized endometriotic cysts showed significantly higher signals compared to those associated with carcinomas, and similarly, higher signals compared to those of the placenta. The solid component of the decidualized endometriotic cyst mainly consists of decidual cells, which possess a more abundant cytoplasm than normal endometrial cells[16]. It is believed this is the main cause of the T2 elongation of the lesion. In contrast, tumor cells in malignancies are characterized by their large nuclei. Thus, the difference in water content between decidualized tissue and cancer tissue is accountable for the higher T2 signals in the decidualized endometriotic cysts...

We also examined the signal intensities of the DWI of decidualized tissues, placentas and carcinomas, but they fail to show significant differences. The susceptibility artifacts and increased motion artifacts caused by the fetus might have influenced the measured SIs. On the basis of these results, it is difficult to assess the usefulness of visual evaluation in DWI. However, the ectopic decidua showed significantly higher ADC value than the carcinomas, and this pattern could allow for a more accurate diagnosis. In the setting of gynecological pathology, a number of studies have sought to differentiate benign lesions from malignant lesions, both uterine and ovarian, using ADC values as a distinguishing parameter [17-19]. One possible explanation for the low ADC value in the malignant tissue could be the restricted water diffusion in tumor cells which feature high N/C ratios[20]. In contrast, decidualized tissues ~~are~~ mainly consist of decidual cells, which contain an abundant cytoplasm. Therefore, the difference in the N/C ratios between decidual and carcinoma cells may be attributed to the significant difference in ADC values between these two disease entities.

Next, we evaluated the SI of the placentas. The placenta primarily consists of villi, which form edematous tissue up to mid-gestation[21]. Although the main component of the placenta is histologically different from the decidualized tissue, the placenta always appears within the field-of-view in MR imaging of the pelvis of pregnant patients, and can be easily detected and compared. Tanaka *et al.* reported one patient case in which the SI of decidualized tissue was similar to that of the placenta on a T2-weighed image[7]. Our study was conducted on a large number of patients and revealed that the decidualized tissue showed significantly higher SI compared to the placenta on T2-weighted images, but similar ADC value to that of the placenta. It remains unclear why the SI of the decidua is higher. Additionally, SI on q T2-weighted image and the ADC value of the placenta are both higher compared to those of

carcinomas. Thus the placenta might serve as a reference in MR imaging for the diagnosis of the mural nodule in the endometriotic cyst up to mid-gestation. On the other hand, the placenta might not necessarily be helpful in later pregnancy, since edematous changes in the placenta are then generally reduced[22].

Repeated intracystic bleedings in endometriotic cysts cause an increased SI of the intracystic fluid in T1-weighted images, and "shading" in T2-weighted images[23]. These imaging characteristics are important for the differentiation of endometriotic cysts from other cystic lesions in the setting of MR imaging. On the other hand, other reports have documented that the intracystic fluid in the malignant transformation of the endometriotic cyst showed lower SI in T1-weighted images[14, 15]. This may be due to an increased excretion of fluid by carcinoma cells[15]. In our study, intracystic fluid also showed significantly lower SI in carcinomas compared to decidualized endometriotic cyst, which is in line with previous reports.

Our results suggest that the combined evaluation of morphological features and signal intensities represents useful criteria to distinguish decidualized tissues from carcinomas.

There are, however, several limitations to our evaluation study. First, the patient profiles of two groups were differed in terms of age distribution and state of pregnancy. However, there was no case of fertile subject with ovarian cancer in our serial MRI studies of the period of study. Secondly, the images used for the evaluation might have been affected by various artifacts, more particularly motion artifacts resulting from fetal movements or physiological bowel movements in the absence of anti-cholinergic drugs. In addition, the smallness of the set ROIs for the solid components of decidualized endometriotic cysts might have enhanced the effect of those artifacts. Secondly, the sizes of the solid components in carcinomas are larger than those of decidualized endometriotic cysts. On the basis of morphological criteria, this could represent an issue, since a very early carcinoma or the tumors of borderline malignancy might also form smaller solid components and be indistinguishable from decidualized endometriosis. Thus, we propose that the combined examination of morphological features and SIs represents a more reliable alternative. Cases of early carcinomas and tumors of borderline malignancy were not included in the present study. Therefore, even when the low-growing component of the endometriotic cyst, as observed in the pregnant woman, is expected to result from a decidualized tissue, it should be carefully monitored until the mass shrinks and disappears. While only two out of 14 cases were histologically proven to be decidualized endometriotic cyst, the other cases were monitored and shrinkage of the solid component was observed. It was

therefore reasonable to establish a clinical diagnosis of decidualized endometriotic cyst.

In conclusion, the presence of endometriotic cysts characterized by a low-growing solid component with high SI on T2-weighted images is highly indicative of decidualized tissues in pregnant subjects and should be monitoring rather than being promptly and surgically sectioned. The higher ADC values found in decidualized tissues and higher SI of the intracystic fluid on T1-weighted images may also be helpful as diagnostic tools. Finally, our results suggest that the SIs of the placenta may serve as a reference for comparison with the solid component of the endometriotic cyst.

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Figure Legends

Figure 1. Maximum heights (mm) of the mural nodules. All mural nodules associated with carcinomas feature larger heights compared to decidualized tissues.

Figure 2. Decidualized endometriotic cyst of rt. ovary in a 29-year-old woman at 13 weeks of gestation. Septated cystic mass is located posterior to the gravid uterus. Sagittal spin-echo T1-weighted image shows (**A**) intracystic fluid with high signal intensity (arrowhead) and mild thickening of the septa with hypointensity (arrows). The solid components on the septa show high signal intensity on T2-weighted image (**B**) and show high ADC value (**C**), while they are poorly visualized on diffusion-weighted image with a b-value of 1000 sec/mm^2 (**D**).

Figure 3. Endometrioid adenocarcinoma associated with endometriotic cyst in lt. ovary of a 64-year-old woman. A large cystic mass with a thick solid component is observed between the urinary bladder and the atrophic uterus.
(**A**) Sagittal spin-echo T1-weighted image presents an intracystic fluid with a lower signal intensity (arrowhead) compared to the fluid presented in **Fig. 2A**. With regard to the signal intensities of the intracystic fluid, T1WI signals were of a lower intensity compared to typical blood. These variations may be due to an increased excretion of fluid from the carcinoma cells. The solid component of the lesion (arrows) shows low signal intensity on T2-weighted image (**B**), low ADC value (**C**), and high signal intensity on diffusion-weighted image with a b-value of 1000 sec/mm^2 (**D**).