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Case Report

Magnetic resonance imaging pitfalls in determining myometrial invasion in stage I endometrial cancer: A case report and literature review ☆

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ABSTRACT

The degree of myometrial invasion (MI) is crucial in the preoperative diagnosis of endometrial cancer (EC) using MRI in terms of therapeutic and prognostic implications. However, several pitfalls should be kept in mind when using this modality. We report a case of EC on a 64-year-old woman, identified preoperatively without MI based on ultrasonography and MRI, implying a low risk of lymph node metastasis; surprisingly, the uterine incision showed the lesion had invaded <50% of the myometrium. Thus, a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy were performed, and histopathologic analysis confirmed that the EC was on stage IA (cancer is in the endometrium only or less than halfway through the myometrium). In our case, thinning myometrium and uterine atrophy due to aging, multiple leiomyomas, previous curettage, and blood clots were all pitfalls for MRI in detecting MI. By detecting tiny or isointense tumors and depicting distinct vascularity of the malignancy in postmenopausal women, functional MRI techniques such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) can help reduce

Abbreviations: EC, Endometrial Cancer; MI, Myometrial Invasion; LNM, Lymph Node Metastasis; MRI, Magnetic Resonance Imaging; USG, Ultrasonography; CT, Computed Tomography; TVUS, Transvaginal Ultrasound; T1WI, T1-Weighted Imaging; T2WI, T2-Weighted Imaging; T1FS, T1-Weighted Fat-Suppressed; DWI, Diffusion-Weighted Imaging; DCE-MRI, Dynamic Contrast Enhanced-Magnetic Resonance Imaging; eGFR, Estimated Glomerular Filtration Rate; JZ, Junctional Zone; SEE, Sub-Endometrial Enhancement; PPV, Positive Predictive Values; NPV, Negative Predictive Values; GRE, 3D FS Gradient-Echo; GdT1WI, Gadolinium-Enhanced T1WI; FIGO, The International Federation of Gynecology and Obstetrics.

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pitfalls when assessing MI. Clinicians can employ DWI preoperatively, which is more reliable and superior to DCE-MRI in determining tumor areas without contrast injection and perform a postoperative histopathological examination to confirm MI in EC.

Globally, endometrial carcinoma (EC) is expected to become the second most common gynecological malignancy in 2020 [1,2]. The emergence of EC in developing countries is tremendous: 26.7/100,000 of people in Asia were diagnosed, and the disease was fatal for 6.1/100,000 people in 2012 [3]. The EC burden constituted 7700 cases and 2600 deaths per year, becoming the third deadliest cancer among women in Indonesia [81]. From 2008 to 2012, our center treated 4248 gynecological oncological cases and 18,216 total cancer cases [5]. EC is most commonly found among postmenopausal women and is detected in the early stage [6]. Several factors promoting higher estrogen exposure, including overweight and/or obesity, metabolic syndrome, polycystic ovarian disease history, and hereditary non-polyposis colorectal cancer, are all risk factors for EC [7,8].

In working up the diagnosis, planning for therapy, and determining the prognosis of EC, it is crucial to obtain accurate myometrial invasion (MI) information to avert the dangers of under-or over-staging [9]. The depth of MI also corresponds to the duration of time until recurrence and the existence of lymph node metastasis (LNM); thus, it is related to different therapy options and prognoses [10–13]. Information on MI can be exclusively acquired preoperatively by imaging techniques, the most standard and beneficial of which is magnetic resonance imaging (MRI) [16], as it can accurately visualize and determine the size of tumors, the extent and degree of MI, LNM, and cervical extension. Additionally, it is adequate at assessing the uterine wall and pelvic structures [1,17,15]. In determining the depth of MI involvement, MRI has proven to be more accurate than ultrasonography (USG) and computed tomography (CT) [10]. However, the detection of MI remains challenging, and several pitfalls are often encountered in clinical practice [8]. We attempted to present a stage I EC case that had a difficult preoperative MI diagnosis. We also added a literature review concerning imaging modalities to evaluate EC and strategies used to minimalize the pitfalls of MRI in detecting MI.

Case Presentation

A 64-year-old woman was referred from a district hospital with a diagnosis of EC. She presented with the chief complaint of postmenopausal vaginal bleeding 2 years before admission to the hospital. The patient underwent a curettage for the thickening of her endometrium 1 month before being referred to our hospital. Her former hospital provided her with a biopsy result that showed a well-differentiated endometrioid adenocarcinoma. For the past 13 years, the patient had been menopausal and had several comorbidities, including hypertension and metabolic syndrome. There was no previous history of cancer in the patient and her family. She had no children.

Investigation

Her vital signs were stable. Her vulva and urethra displayed no apparent abnormalities, and her genitalia were examined with the speculum and found to be within normal limits. A vaginal toucher showed no palpable adnexal mass, no vaginal anomalies, and a standard uterus size; however, a portion was atrophied. A digital rectal examination revealed good tonus of the anal sphincter, smooth rectal mucosa, no collapse of the rectal ampulla, and no palpable mass. The patient was 70 kg and 155 cm and was classified as obese. The most notable laboratory findings were increased lactate levels (5.5 mmol/L) and slightly increased procalcitonin levels (1.09 ng/mL). In addition, the blood urea nitrogen level (24 mg/dL), creatinine level (0.8 mg/dL), eGFR (82 mL/min/1.73m^2), and random blood sugar (101 mg/dL) of this patient were identified normal.

The patient underwent a chest X-ray, USG, and MRI of the pelvis and lower abdomen. Cardiomegaly, aortic elongation, calcification infiltrates in the lower right lung field suspected of pneumonia (which disappeared following treatment), and thoracic scoliosis were all seen on a chest X-ray. A transvaginal ultrasound (TVUS) examination (Fig. 1) showed an echogenic area with irregular edges and endometrial–myometrial junction, which appeared as a polypoid mass in the uterine cavity with a dimension of 36 × 27 mm, originating from thickening of the endometrial wall (a suspected malignancy) with no penetration to the serosa and myometrium. There was also a well-defined hypoechoic area in the lower-left uterine segment that was 30 mm in diameter and originated from a suspected intramural uterine myoma. The uterus was retroflexed with a regular shape but slightly enlarged size. The endocervix and portion were typical, and both ovaries were regular in shape and size. No abnormal mass was seen in both adnexa. The liver and both kidneys were normal, and there were noy ascites.

We scheduled our patient for an MRI examination a week after TVUS was conducted. The pelvic and lower abdomen MRI in Figure 2 depicted an irregular solid mass, hypointense on T1-weighted imaging (T1WI), iso-hyperintense on T2-weighted imaging (T2WI), with contrast enhancement, measuring approximately 5.1 × 3.5 × 4.5 cm inside the uterine cavity. There was no visible mass extension to the myometrium, cervical stroma, and uterine serosa. There was no pelvic lymph node enlargement. The right and left adnexa were normal.

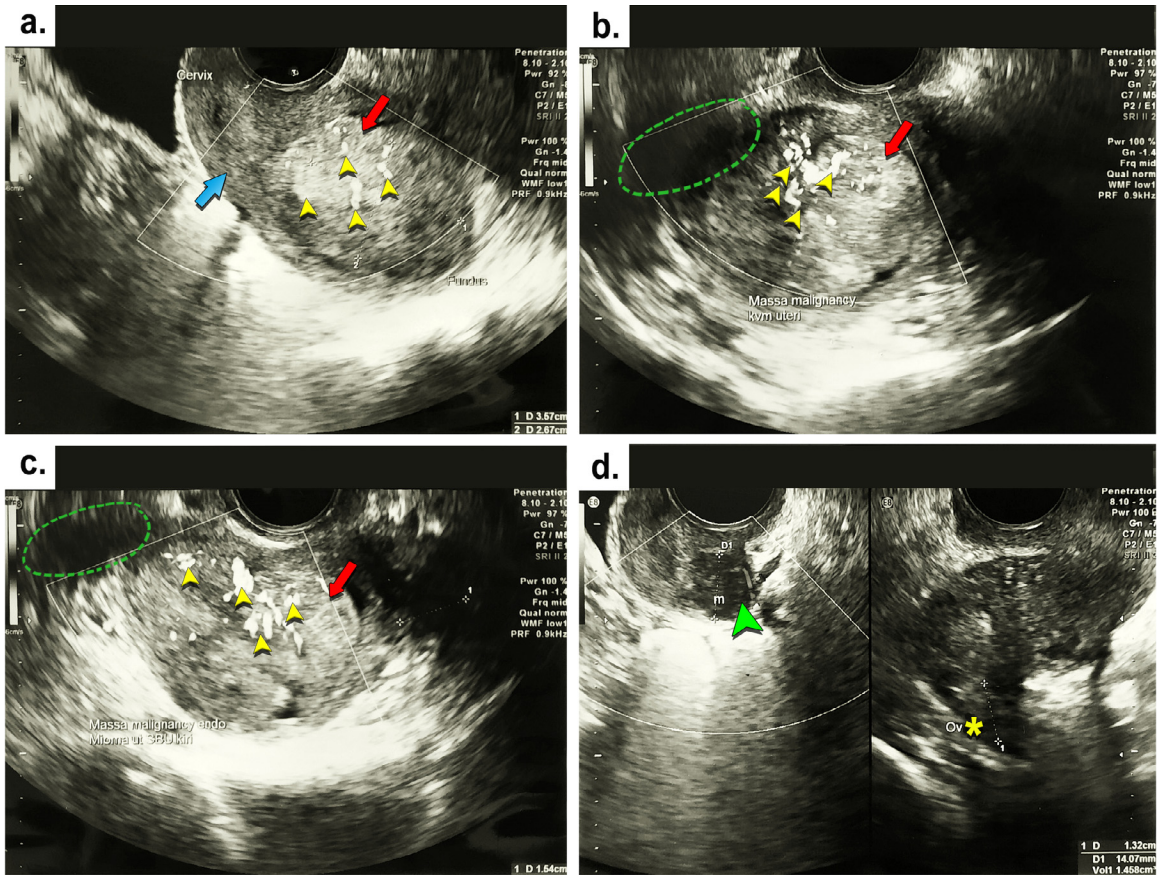

Fig. 1 – Transvaginal ultrasound (TVUS) findings. (A) A blue arrow shows the endometrium with the cervix at its tip. The image was visualized as a retroflexed uterus with a standard shape but slightly enlarged size. The endocervix and the cervical portion were within normal conditions. (A-C) The red arrow identifies an echogenic mass in the uterine cavity with a dimension of 36 x 27 mm and irregular edges originating from a suspected malignancy of the endometrial wall that had not penetrated the serosa and myometrium. The multiple yellow arrowheads indicates blood flow. (B, C) The shape indicated with the green dotted line depicts the possible location of the myoma. (D) A green arrowhead presents a well-defined hypoechoic mass in the lower-left uterine segment, 30 mm in diameter, which is suggested to be from an intramural uterine myoma. A yellow asterisk indicates a normal right ovary with no suspicious adnexal mass. (Color version of figure is available online.)

A review of biopsy results from the prior hospital taken a week before the patient's admission to our center was consistent with grade I, well-differentiated endometrial carcinoma. A pap smear for the patient in our institution revealed no cervical lesions and suspected malignancy.

Treatment

The patient underwent a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. Furthermore, patient was prescribed antibiotics (ie, intravenous Cefazolin 1 × 2 g) and premedications (eg, H_2 blockers and antiemetic) before surgery. A rectovaginal examination under narcosis demonstrated a normal uterus and no palpable mass on both adnexae. Intraoperatively, on laparoscopic view, the uterus was discovered to be typical, and both ovaries and tube were normal. The peritoneum wall was normal, and the liver and spleen were also typical. Colpotomy was performed at the border of the portion, and the uterus was taken out vaginally. Uterine incision showed that the lesion had invaded less than 50% of the myometrial wall (Fig. 3).

Definitive Diagnosis

The histopathology results from the hysterectomy specimen showed round tumor cells with mild pleiomorphic nuclei, cellular vesicles, some with nucleoli, and eosinophilic cytoplasm. Mitotic cells were also found. The stroma was fibrovascular and filled with lymphocytes and neutrophils. The tumor mass invaded the myometrium at less than 50% of the myometrium thickness; therefore, the diagnosis after histopathology was grade IA well-differentiated endometrial carcinoma. No lymphovascular invasion or tumor implantation were found on the surface epithelium and stroma of the

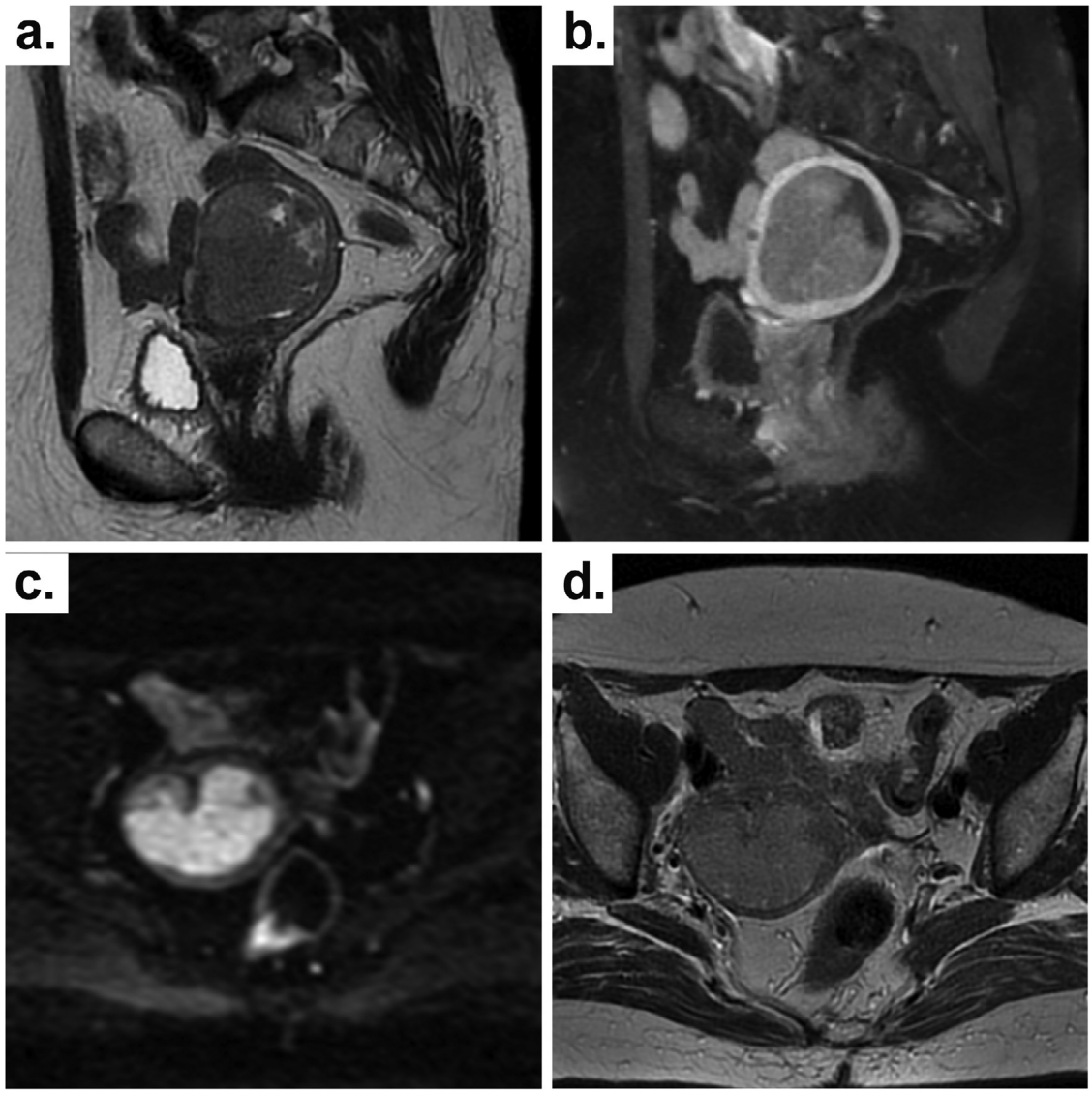

Fig. 2 – Pelvic and lower abdominal magnetic resonance imaging (MRI) examination in (A) sagittal T2 weighted image (T2WI) view and (B) sagittal T1-weighted fat-suppressed (T1FS) + contrast show the intrauterine cavity's solid and irregular mass without myometrial invasion. There were no signs of serosal invasion or cervical stromal invasion. (C) Axial diffusion-weighted imaging (DWI) on b=1000m/s and (D) axial T2WI show intrauterine cavity solid mass with high diffusion restriction confined to the uterine cavity. There were no signs of lymph node enlargement in the pelvic region.

cervix, bilateral ovaries, bilateral tubes and/ or fimbriae, and bilateral parametrium. In macroscopic examination, tissues grossly appearing as withish nodules ranging from 0.5 to 0.6 cm in diameter were found to be uterine leiomyoma and bilateral paratubal cysts with diameter of 0.5 cm containing clear fluid were also found.

Prognosis, Follow Up, and Outcome

Postoperative treatment constituted cefixime 2 × 100 mg for 8 days. Two days after surgery, the patient responded adequately, and her condition improved day by day. No infections were observed, and the patient's symptoms had subsided. She was discharged from the hospital 7 days after her operation. Here family members were also given a short educational talk regarding disease prognosis and the importance of follow-up. Two weeks after being discharged, the patient visited the outpatient clinic. No sequelae to the symptoms were reported. The incision wound was perfectly closed with no sign of inflammation. We evaluated her postoperative TVUS: the abdomen and pelvis conditions were shown to be typical. She went back to her daily activities a month after being discharged.

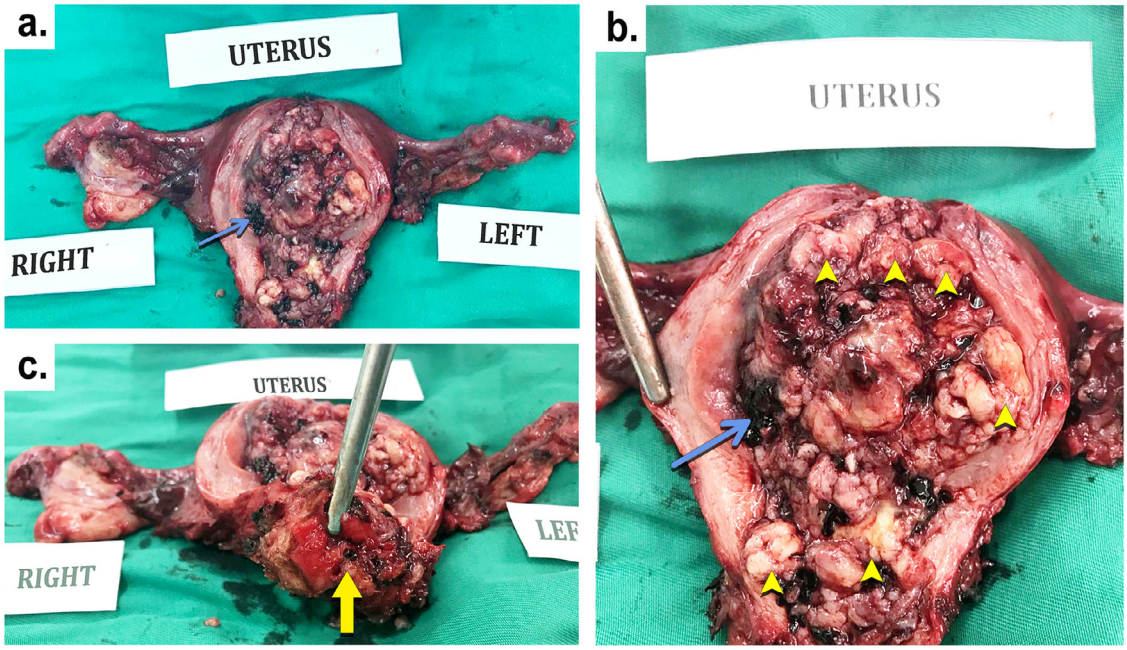

Fig. 3 – Gross appearance and cut surface of the uterus with endometrial cancer and leiomyoma. (A) The blue arrow indicates endometrial cancer and shows the mass infiltrating myometrium with less than 50% myometrial thickness. (B) Multiple yellow arrowheads demonstrate multiple leiomyomas. (C) The yellow arrows depict cervical sections. (Color version of figure is available online.)

Discussion

Approaching Endometrial Cancer and MRI Use for Myometrial Invasion Assessment

In our case, the patient's endometrium was initially evaluated with TVUS. This TVUS had an overall sensitivity of 68.4% in predicting the depth of MI and an accuracy rate of 77.5% [26]. Under TVUS (Fig. 1), MI was captured as an iso-hyperechoic image, signifying tissue invasion resembling the adjacent myometrium [32]. It is usually easy to distinguish; sometimes, however, it can only be estimated from irregularities in the junction between the endometrium and myometrium [27]. To circumvent this limitation of TVUS, we used MRI as a practical modality in identifying the existence of MI and local tumor staging in the preoperative assessment of EC [11]. MRI was more effective than TVUS and CT at detecting deep MI [15,28]. This modality is preferred due to its great contrast, excellent spatial resolution, and lack of radiation, making it an ideal diagnostic tool to assess the female pelvis by depicting the uterine wall in separate layers [15].

The MRI results suggested that the surrounding myometrium was comprised of 2 separate layers. The junctional zone (JZ) is the innermost myometrial layer (archimyometrium and/or stratum subvasculature and/or subendometrial halo) that lies close to the endometrium. In TVUS, it appears as a low-intensity signal band (hypoechogenic); meanwhile, in MRI, it appears as hypointense on T2WI [35]. On the other hand, the external myometrium layer has a more irregular appearance, but it is typically an intermediate-intensity signal [35]. On T2WI, EC has an intermediate signal intensity and is hyperintense compared to adjacent myometrium [35]. MI is interpreted on T2WI as a disturbance or peculiarity of the low-intensity signal JZ as an essential landmark [36]. Our patient's MRI results (Fig. 2) showed a mass with irregular edges, which is iso-to-hyperintense in signal intensity on T2WI [37,38]. After contrast injection, the inner myometrial layer or JZ is enhanced uniformly during the earlier dynamic phase as a continuous band or a "sub-endometrial stripe" [38]. This sub-endometrial stripe disruption of JZ indicated MI, and an intact JZ ruled out deep MI in TW2I (Figs. 2A and D) and a continued string of early sub-endometrial enhancement (SEE) depicted in Figure 2B [35]. The depth of MI is best assessed on the axial oblique plane, which is acquired perpendicular to the endometrial cavity, as shown in Figures. 2C and D [33].

The presentation of a complete SEE on T1WI with contrast and/or the low T2WI signal disruption of JZ with <50% myometrial invasion are indicators of stage IA EC. Meanwhile, irregularity or disruption of the poor T2WI signal in JZ and/or SEE after contrast injection in T1WI with MI ≥50% of myometrial depth is the basis for the diagnosis of stage IB EC [39,40]. Our patient was misdiagnosed without MI preoperatively but was proven to have MI <50% after surgery via histopathology. Cumulative MRI results have found that MI was accurately identified in 66.67% of cases, with overestimation and underestimation occurring in 13.89% and 8.3% of cases, respectively [20]. The negative predictive values (NPV) for the presence of MI is poor (72%), implying that conventional MRI alone can not exclude pathological MI [11,20]. Furthermore,

the depth of MI in patients with EC is directly related to prognosis, recurrence, and the presence of LNM [10,11]. In cases where LNM is at stake, a false-negative MI detection may lead to the use of only conservative surgical procedures (eg, trans-vaginal or trans-abdominal hysterectomy without lymphadenectomy) [41]. Meanwhile, false-positive detection leads to riskier surgery procedures (eg, radical hysterectomy: removal of the uterus, cervix, the upper part of the vagina, and nearby tissues, along with pelvic lymphadenectomy and a bilateral salpingo-oophorectomy for postmenopausal patient), increasing the risk of harm to patients who might not benefit from a lymphadenectomy in the first place [50,55]. Ultimately, when we conducted surgery on this patient, we found that her MI constrained us to total laparoscopic hysterectomy and bilateral salpingo-oophorectomy procedures.

Pitfalls of MRI in Evaluating Myometrial Invasion of Endometrial Cancer

In this case, we identified a thinning myometrium and uterine atrophy, multiple leiomyomas, previous curettage, and blood clots as plausible factors that may have contributed to the inaccurate prediction of MI. Our patient had a more obscured JZ as a menopausal and geriatric woman, particularly 1 over 55 years old [57]. JZ may not be well-measured as a marker of MI detection in approximately 30% of postmenopausal women [56]. Due to aging and uterine atrophy, her myometrium and endometrium thinned, hampering the visualization of tumor invasion [38]. In T2WI, the signal from the outer boundaries of the myometrial tissue was also weakened, making the JZ more challenging to distinguish, potentially leading to MI misdiagnoses [36,38].

Multiple leiomyomas, confirmed by histopathology and TVUS in our patient, were another obstacle to distinguishing MI in EC. Patients with multiple leiomyomas may disrupt the endometrial-myometrial interface leading to misdiagnosis, as seen in this presented case [15,10,43,58]. Some leiomyomas may exhibit restricted diffusion, and the presence of leiomyomas is a well-known artifact that decreases accuracy of MI detection in EC [57].

Curettage procedures before MRI may attenuate the myometrium in elderly patients who had thin myometria in the first place. This has contributed to the non-visualization of the mass and the challenge of assessing the depth of MI in MRI [50]. During curettage, masses may have diminished or removed [10]. Endometrial mass is confined to the uterine corpus and limited to the endometrium in stage IA. Hence, smaller stage IA tumors may be concealed after curettage or biopsy procedures [62]. In addition, endometrial cavity distension caused by the accumulation of blood clots or fluids, as illustrated in the macroscopic findings of Figure 3, may also become another threat in visualizing the anatomical detail of the uterus in our patient's MRI [10].

Overcome the Pitfalls of MRI in Determining Myometrial Invasion

Diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) are 2 functional tests of MRI that can help overcome the MI pitfalls associated with conventional MRI [33]. DWI and DCE-MRI sequences deliberate transformations in the oxygenation, perfusion, and tissue physiology of tumor microstructure, yielding quantitative and semi-quantitative characteristics that can be used as biomarkers of tumor features [8]. This dynamic study is beneficial for depicting EC cases when the JZ is not visible due to tumors and the myometrium's unusual vascularity, distinguishing it from fluid loading in the endometrial cavity [10]. DCE images are secured using a 3D FS gradient-echo (GRE) T1WI sequence after an intravenous 0.1 mmol/kg gadolinium injection at a 2–3 mL/s rate [8]. DCE-MRI or gadolinium-enhanced T1WI (GdT1WI) has been shown in the literature to be a promising imaging modality for predicting invasion depth of EC in postmenopausal women, as seen in our patient (Fig. 2B) [66]. On the DCE sequence, small tumors may display earlier enhancement than the normal endometrium and slower enhancement than the myometrium. These tumors may appear hypointense in their earlier phases than in myometrium [64].

DCE-MRI has a better diagnostic performance for MI detection than CT or TVUS [38]. DCE-MRI can assist conventional T2WI in determining the depth of MI [40]. However, contrast agent injections are mandated for DCE-MRI, which is contraindicated for people with gadolinium-containing agent allergies, are pregnant, or have extreme renal failure [46]. DWI has an advantage over DCE-MRI due to the former not involving contrast agent injection and having a shorter procedural time [51]. DWI is a functional imaging strategy that portrays information about water mobility, tissue cellularity, and cellular membrane integrity. DWI is required because EC exhibits limited diffusion to surrounding tissue. This is exemplified in the higher intensity signals of DWI [51]. EC can be depicted with DWI as areas of increased signal intensity relative to the surrounding hypointense myometrium [67]; thus, DWI can aid in the diagnosis of MI . DWI had slightly higher diagnostic accuracy (94.3% vs 88.6%), a slightly greater specificity (95.5% vs 86.4%), and the same level of sensitivity (92.3%) as DCE-MRI in assessing the depth of MI [37]. The positive predictive values (PPV) and NPV of DWI were 52.4% and 92.3%, superior to DCE-MRI, which had corresponding PPV and NPV values of 40.9% and 84.0%, respectively [16]. A study in Indonesia confirms the excellent sensitivity of DWI (94.12%) but moderate specificity (64.71%) in assessing MI to detect individuals with deep MI [68].

Beddy et al. [51] suggest that DWI is more precise in assessing gynecological malignancy based on the International Federation of Gynecology and Obstetrics (FIGO) staging and might potentially replace DCE-MRI in the presurgical staging of EC [70]. DWI is also superior to DCE-MRI in reliability and reproducibility [71]. DWI has an accuracy of 94%, while DCE-MRI was 88% for confirming deep MI [16,51,73,74]. DWI might be more beneficial for our case because it can estimate the depth of MI in the condition of coincident leiomyoma [43]. Nonetheless, the complementary pairing of both DWI and Gd is recommended to evaluate the depth of MI. Fused T2WI and DWI may also be valuable, as they simultaneously provide the tumor's anatomic and functional details [65,79]. Compared to T2WI alone, this fusion modality has satisfactory results in gynecological cancer [79]. Complementary GdT1WI or DCE-MRI should be used if the depth of MI is equivocal on T2WI and

DWI. Nevertheless, although we have minimized the pitfalls by performing GdT1WI and DWI simultaneously, the presence of MI is still missed, potentially because our patient's characteristics impede the interpretation of MRI. This case suggests that postoperative histopathology examination is still the best confirmation method; thus, the turnaround time of its results is essential.

Strengths and Limitations of Presented Case and Patient's Perspective

Our case has some limitations. The interobserver agreement between the radiologists was not evaluated in this case presentation. Curettage procedures in the patient's prior hospital may have caused a thin myometrium and affected the imaging results. In this case, we also did not perform CT for the sake of cost-effectiveness following the national insurance scheme. Despite these limitations, our patient received adequate and proper treatment for her MI and EC. Moreover, the patient saw prompt diagnosis and excellent therapy at our hospital as well as low-cost service from the national health insurance scheme. Our patient received a valuable and beneficial treatment that allowed her to recover from stage IA EC.

Conclusion

In working up the diagnosis of EC, it is crucial to obtain accurate MI information preoperatively while drawing up an EC diagnosis to avoid improper staging as it is linked to recurrence, the presence of LNM, the necessity of different therapy, and the implication of prognosis. Preoperative MRI is a beneficial and accurate imaging method for staging EC, allowing for a less invasive surgical approach and lower perioperative morbidity, particularly in older patients with multiple comorbidities. Although MRI is the most standard and helpful imaging modality for EC, several pitfalls may arise from age (due to uterine atrophy), leiomyoma, prior curettage procedures, blood clots, and motion artifacts that may have led to under staging. Therefore, the clinician should be aware of and overcome these errors through further investigation. To compensate for the shortcomings of the isolated use of MRI, DWI can be a vital imaging tool that may encourage the precise staging of EC and eliminate the need for DCE-MRI. DWI is particularly beneficial in tumors that are either iso-intense or hyperintense relative to the myometrium or when the use of a contrast agent is contraindicated. DWI would also render shorter assessment times, leading to a more efficient MRI. Moreover, postoperative histopathological analysis has become the most reliable method of confirming MI.

Patient consent

As the authors, we declare and take a full responsibility that the patient has given her consent and permission to Dr. Cipto Mangunkusumo Hospital for using her images, duplicating her digital photos, or other clinical information relating to her case for the purpose of therapeutical, educational, and/or research. The patient has also given permission to publish her case in scientific medical journals with the title "Magnetic Resonance Imaging Pitfalls in Determining Myometrial Invasion in Stage I Endometrial Cancer: A Case Report and Literature Review" or distribute her case in materials for electronic and printed marketing services, websites, or other communication media with de-identified details. The patient has given her consent and permission for publication with de-identified details. The consent form can be retrieved upon request from the Editors. The CARE guidelines were followed for the writing of this case report.

Author Contribution

Conceptualization: Hariyono Winarto, Muhammad Habiburrahman, Data curation: Hariyono Winarto, Muhammad Habiburrahman, Formal Analysis: Hariyono Winarto, Muhammad Habiburrahman, Funding Acquisition: Hariyono Winarto, Investigation: Hariyono Winarto, Kartiwa Hadi Nuryanto, Trifonia Pingkan Siregar, Methodology: Hariyono Winarto, Muhammad Habiburrahman, Project Administration: Muhammad Habiburrahman, Resources: Hariyono Winarto, Kartiwa Hadi Nuryanto, Software: Muhammad Habiburrahman, Supervision: Hariyono Winarto, Kartiwa Hadi Nuryanto, Trifonia Pingkan Siregar, Validation: Hariyono Winarto, Kartiwa Hadi Nuryanto, Trifonia Pingkan Siregar, Visualization: Muhammad Habiburrahman, Writing – original draft preparation: Hariyono Winarto, Muhammad Habiburrahman, Writing – review & editing: Hariyono Winarto, Muhammad Habiburrahman, Kartiwa Hadi Nuryanto, Trifonia Pingkan Siregar.

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