



Atypical endometrial hyperplasia diagnosed by hysteroscopic photodynamic diagnosis using 5-aminolevulinic acid

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ABSTRACT

Endometrial cancer is diagnosed by endometrial biopsy, imaging and hysteroscopy, but it is sometimes difficult to find small lesions. 5-aminolevulinic acid (5ALA) forms protoporphyrin IX, which accumulates in tumors and fluoresces upon light irradiation. 5ALA is used for photodynamic diagnosis (PDD) for detecting malignant diseases. A 60-year-old female was suspected to have endometrial cancer by magnetic resonance imaging. Endometrial biopsy was performed repeatedly, but no malignant lesion was detected. We performed hysteroscopic 5ALA-PDD and could detect a small lesion. The lesion was excised and diagnosed as atypical endometrial hyperplasia histopathologically. This is the first report that showed hysteroscopic 5ALA-PDD can contribute to diagnosis of early-stage neoplastic lesion in the uterine cavity.

1. Introduction

Endometrial cancer ranks highest among gynecological malignancies. Dilatation and curettage (D&C) is performed to examine endometrial cancer; however, less than half of the uterine cavity is evaluated in approximately 60% of D&C procedures, which results in false-negative diagnoses [1]. Magnetic resonance imaging (MRI), computed tomography (CT), and hysteroscope are also commonly used for diagnosis of endometrial cancer. However, MRI and CT cannot detect lesions of less than a slice in size. Diagnosis of malignant disease by hysteroscopic observation has limitations and the sensitivities for detection of endometrial hyperplasia and cancer are 56.3% and 80.0%, respectively [2].

Photodynamic diagnosis (PDD) using 5-aminolevulinic acid (5ALA) has been used as a diagnostic procedure for malignant disease. 5ALA is a precursor of protoporphyrin IX (PpIX), which accumulates in tumor cells. PpIX emits red fluorescence when irradiated with blue excitation light. Malignant tumor cells can be detected based on these characteristics of PpIX. Wyss et al. [3] examined lesions in the uterine cavity using a hysteroscope and showed that endometrial cancer and hyperplasia were detectable with 5ALA-PDD.

Here, we report the case of a patient with suspected endometrial cancer with myometrial invasion on MRI, but with no malignant lesion in endometrial biopsy, who was diagnosed with atypical endometrial hyperplasia (AEH) using hysteroscopic 5ALA-PDD.

2. Case

The patient was a 60-year-old female with no history of pregnancy or delivery, with menopause at age 50 years. She underwent MRI at another hospital for comprehensive medical examination and was suspected to have endometrial cancer, after which she visited our hospital. Endometrial biopsy was performed several times, but no malignant lesion was detected. MRI in our hospital led to diagnosis of suspected endometrial cancer invading more than half of the myometrium at the corner of the right oviduct (Fig. 1). Serum carbohydrate antigen (CA)-125 and CA19-9 were elevated to 40 U/ml and 92 U/ml respectively (normal, CA125 < 35 U/ml, CA19-9 < 38 U/ml).

Performance of hysteroscopic PDD with 5ALA was approved by the ethics committee of Keio University School of Medicine. After confirming that the patient met the inclusion criteria for the protocol and did not meet the exclusion criteria (Table 1), the method was explained to her and she provided informed consent. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0, Japanese Clinical Oncology Group (JCOG) version.

Three hours before surgery, 5ALA hydrochloride (provided by SBI Pharmaceuticals Co., Ltd., Tokyo, Japan) was dissolved in water at a dose of 20 mg/kg and orally administered. Subsequently, hysteroscopic uterine cavity biopsy was performed under lumbar anesthesia. A D-Light System (Karl Storz SE & Co. KG, Tuttlingen, Germany) that included a D-Light C light source, a Tricam SL II camera control unit, a Tricam-P PDD camera head, and a Hopkins II Forward-Oblique telescope (30°) was

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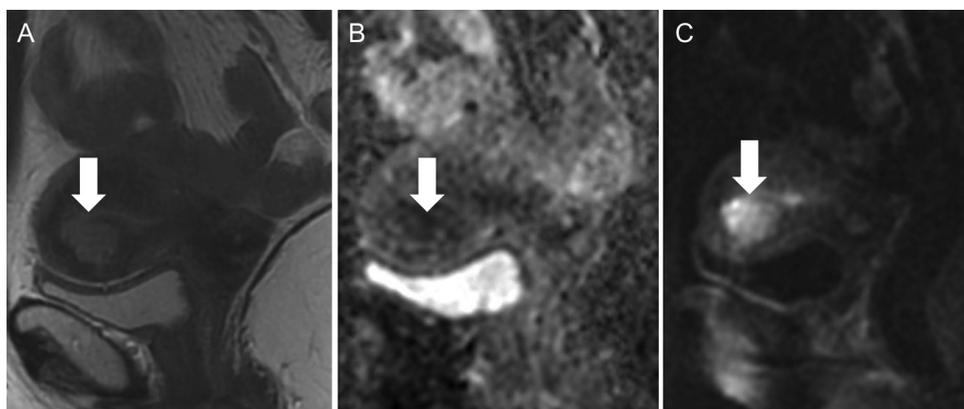


Fig. 1. Magnetic resonance imaging (MRI) findings. (A) Sagittal T2-weighted image (T2WI). (B) Apparent diffusion coefficient (ADC) mapping. (C) Sagittal diffusion-weighted image (DWI). A tumor lesion (arrow: 1.8 cm in width) in the anterior wall of the uterine body had a low signal on ADC and a high signal on DWI, and consequently was suspected to have a high cell density. MRI showed that the junctional zone was interrupted, and endometrial cancer was suspected to have myometrial invasion more than half of the myometrium.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	
1.	Patients who have diseases in uterine cavity.
2.	Patients who plan to undergo hysteroscopic operation for those diseases at the department of obstetrics and gynecology of Keio university hospital.
Exclusion criteria	
1.	Under 20 years old
2.	BMI > 30
3.	The medical history of endometrial entirely curettage in recent 14 days.
4.	The allergic history for the analog of the porphyrin.
5.	Porphyria
6.	The medicine that is known for the cause of photosensitivity (ex. tetracycline antibacterial agent, medicine of sulfonamide, new quinolone antibacterial agent, hypericin and St. John's Wort).
7.	The possibility of pregnant or breast feeding.
8.	The diabetes mellitus and/or hyperlipidemia which is not controlled.
9.	Other endocrine diseases which are not controlled.
10.	Considered inadequate for this trial by the principal investigator

used for 5ALA-PDD. No marked lesion was found by hysteroscopic observation of the uterine cavity with white light, but a small PDD-positive lesion was detected in the fundus (Fig. 2A,B). The PDD-positive tissue was resected hysteroscopically and examined by histopathology. The uterine cavity at the corner of the right oviduct, which was suspected to have lesions on MRI, was PDD-negative (Fig. 2C,D). The endometrium around the right oviduct was resected including the myometrium, and examined by histopathology. Nausea (Grade 1) developed before surgery after oral administration of 5ALA, but disappeared immediately after surgery. No other adverse events occurred. The patient was discharged on postoperative day 1.

Histopathological examination led to a diagnosis of AEH for the PDD-positive tissue (Fig. 2E). In contrast, the specimen resected from the uterine cavity around the right oviduct, which was suspected to be cancer on MRI, showed no histopathologically malignant findings. Though we recommended hysterectomy to the patient, she didn't agree with hysterectomy. She was undergoing observation closely.

3. Discussion

Lesions in the uterine cavity were detected by hysteroscopic 5ALA-PDD, leading to diagnosis of AEH. Wyss et al. performed 5ALA-PDD in 44 patients with endometrial cancer who were scheduled to undergo hysteroscopy and collected 60 specimens using total endometrial curettage and targeted biopsy [3]. Wyss et al. found PDD-positive specimens in patients diagnosed with endometrial cancer and AEH [3]. These results suggest that hysteroscopic 5ALA-PDD has potential for identification of diseases for which hysterectomy is indicated, including endometrial cancer and AEH. However, the diagnostic sensitivity and specificity of this approach is unknown.

Though she was suspected to have endometrial cancer with

myometrial invasion at the corner of the right oviduct on MRI before surgery, we could not identify a lesion there by hysteroscopy with white light nor PDD. We did endometrial biopsy around there, but the specimen showed no malignant findings histopathologically. According to the hysteroscopic findings and MRI findings, there is a possibility of a neoplastic diseases such as malignant transformation of adenomyosis [4]. We should strongly recommend hysterectomy to the patient if the tumor size is increased or the tumor markers (CA125 and CA19-9) level are elevated during follow-up period.

Endometrial cancer and AEH are increasing in young women and fertility preservation treatment is important for these patients. However, uterine cavity-targeted procedures such as repeated total endometrial curettage affect pregnancy and also have a high recurrence rate [5]. 5ALA-PDD, as used for our patient, is currently used as cystoscopic PDD in urological practice. In a comparison of malignant lesions in the bladder resected by cystoscopy associated with PDD and under normal white light, the relapse-free period was significantly longer in the PDD group [6]. PDD permitted identification of difficult lesions, leading to increased total resection of lesions due to the visible resection margin. There are few studies on the utility of hysteroscopic PDD, but these findings suggest that this method can identify small and local lesions, which is likely to contribute to decreased recurrence and improved fertility preservation in treatment in the uterine cavity for patients with endometrial cancer and AEH.

4. Conclusion

In this case, hysteroscopic 5ALA-PDD was used to diagnose atypical endometrial hyperplasia by identification of a small lesion in a patient without this diagnosis preoperatively. This is the first report that showed hysteroscopic 5ALA-PDD can contribute to diagnosis of early-

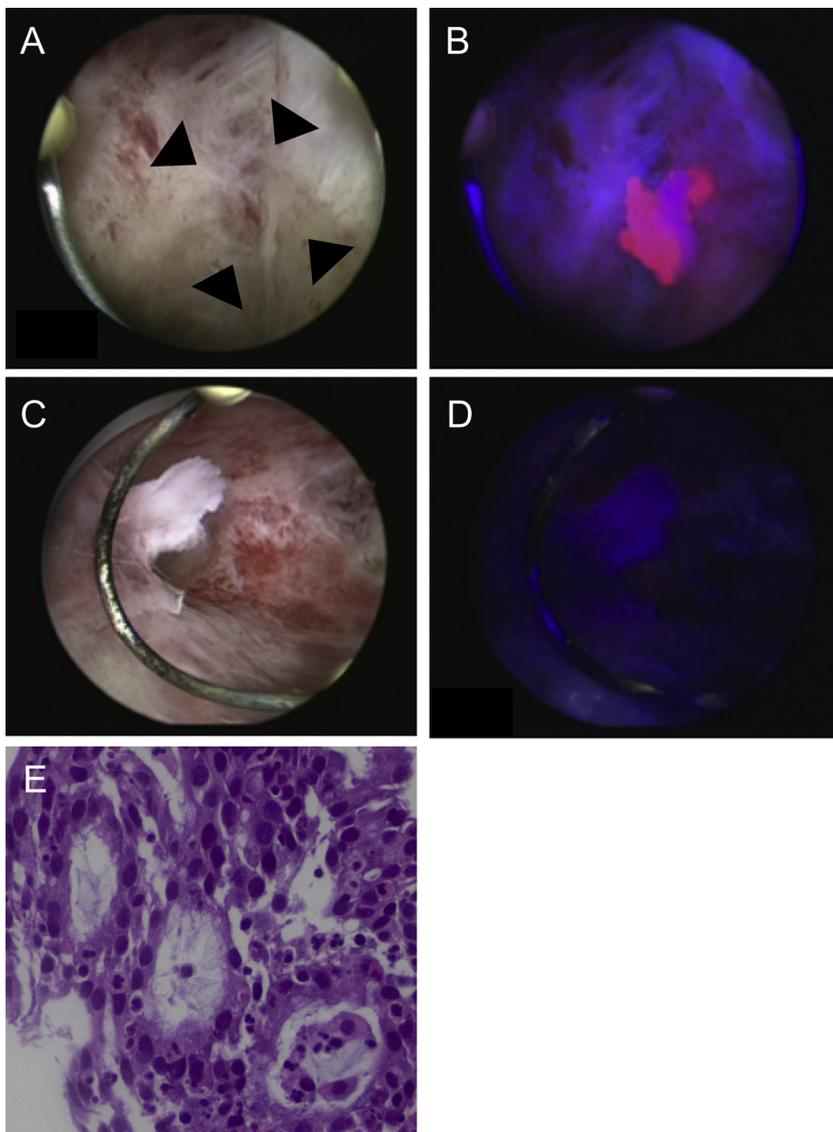


Fig. 2. (A) Hysteroscopic findings for the uterine cavity with white light. (B) Hysteroscopic findings for the uterine cavity under photodynamic diagnosis (PDD). (C) Uterine cavity around the right oviduct with white light. (D) Uterine cavity around the right oviduct under PDD. (E) Histopathological findings from hematoxylin-eosin staining (x400).

It was difficult to identify a lesion in the uterine fundus with white light, but lesions were detected by PDD. Arrow heads at fig. A show the same part of PDD positive lesion under white light. No marked PDD-positive tissues were detected at the corner of the right oviduct, in which a lesion was suspected before surgery. Histopathological findings of the PDD positive lesions from hematoxylin-eosin staining showed that proliferation of atypical endometrial glands was found, but there was no nuclear atypia indicating cancer. Consequently, the patient was diagnosed with atypical endometrial hyperplasia.

stage neoplastic lesion in the uterine cavity. Further studies are needed to examine the diagnostic sensitivity and specificity of this method.

Conflicts of interest

5-Aminolevulinic acid hydrochloride was provided free by SBI Pharmaceuticals Co., Ltd., Tokyo, Japan. A hysteroscope was also provided free by MC Medical, Inc., Tokyo, Japan.

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