Photodiagnosis and Photodynamic Therapy 27 (2019) 295–297

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Case report

Atypical polypoid adenomyoma treated by hysteroscopy with photodynamic diagnosis using 5-aminolevulinic acid: A case report

Yusuke Matoba, Kouji Banno*, Yusuke Kobayashi, Iori Kisu, Daisuke Aoki

Keio University School of Medicine, Department of Obstetrics and Gynecology, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan

ARTICLE INFO

Keywords:
5-Aminolevulinic acid
Atypical polypoid adenomyoma
Hysteroscopy
Photodynamic diagnosis

ABSTRACT

Surgical resection for atypical polypoid adenomyoma (APA) is an option for fertility preservation. Due to the high recurrence rate of APA, studies have been conducted to improve total resection of tumors. Photodynamic diagnosis (PDD) using 5-aminolevulinic acid (5-ALA) improves tumor resection, but this has not been applied for APA. The patient was 35-year-old. After initial treatment, the APA lesion did not disappear. We performed hysteroscopic tumor resection using 5-ALA-PDD. Only one PDD-positive lesion was found and histopathologically diagnosed as APA. Other areas were PDD-negative and showed no histopathologic APA or malignant findings. This is the first report of hysteroscopic 5-ALA-PDD for APA. This method makes it easy to identify morbid lesions, and may lead to improved total resection and decreased recurrence.

1. Introduction

Atypical polypoid adenomyoma (APA) is a benign polypoidal tumor that includes both epithelial and mesenchymal lesions. Histopathological findings of APA show close mixing of atypical endometrial glands and smooth muscles. Consequently, APA should be differentiated from endometrial polyp, submucosal leiomyoma, endometrioid adenocarcinoma, adenosarcoma, and carcinosarcoma. Furthermore, APA is sometimes accompanied by atypical endometrial hyperplasia and endometrioid carcinoma, and is therefore a disease that requires attention.

The common onset age of APA is around 40 years old. No treatment protocols have been established. Patients who do not desire fertility preservation are treated by total hysterectomy, while those wanting fertility preservation undergo partial surgical resection, including hysteroscopic tumor resection and dilation and curettage (D&C), and hormone therapy with high dose medroxyprogesterone acetate (MPA). However, the recurrence rate of APA is high and malignant tumors may subsequently develop. Therefore, follow-up after initial treatment is essential. Treatment protocols to improve total resection and maintenance therapy with hormones are under examination [1].

5-aminolevulinic acid (5-ALA) is a photosensitizer that accumulates in tumors and converted to protoporphyrin IX (PpIX). PpIX emits red fluorescence when irradiated with blue excitation light. Photodynamic diagnosis (PDD) of tumors using these characteristics has been used for detection of malignant tumors, including bladder cancer, and shown to contribute to improved lesion resection. Here, we report the case of a patient with APA who underwent hysteroscopic tumor resection using 5-ALA-PDD.

2. Case

The patient was a 35-year-old nulliparous female. She was diagnosed with APA during infertility treatment at another hospital and was then referred to our hospital. The patient underwent hysteroscopic tumor resection of APA, after which she was treated with MPA. She then required hysteroscopic tumor resection again because remaining APA was found by endometrial biopsy. Preoperative magnetic resonance imaging could not find any endometrial lesion.

Performance of hysteroscopic PDD with 5-ALA was approved by the ethics committee of the Keio University School of Medicine (approval No. 20170318). The inclusion criteria and the exclusion criteria are shown on Table 1. The method and information about hysteroscopic 5ALA-PDD was explained to the patient and she provided informed consent. Adverse events were graded according to the Common Terminology Criteria for Adverse Events v.4.0.

Three hours before surgery, 5-ALA hydrochloride (SBI Pharmaceuticals Co., Ltd., Tokyo, Japan) was dissolved in water at a dose of 20 mg/kg and administered orally. 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 used for 5-

* Corresponding author at: 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan.
E-mail address: kbanno@z7.keio.jp (K. Banno).

https://doi.org/10.1016/j.pdpdt.2019.06.019
Received 24 April 2019; Received in revised form 7 June 2019; Accepted 24 June 2019
Available online 25 June 2019

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Disease in uterine cavity.
	Scheduled hysteroscopy for this disease at the Department of Obstetrics and Gynecology of Keio University Hospital.
Exclusion criteria	< 20 years old
	BMI > 30 kg/m^2
	Endometrial curettage in the last 14 days
	History of allergy for porphyrin analogs
	Porphyria
	Taking drugs known to cause photosensitivity, such as tetracycline antibacterial agents, sulfonamides, new quinolone antibacterial agents, hypericin, and St. John's Wort
	Possibility of pregnancy or current breast feeding
	Diabetes mellitus and/or hyperlipidemia that is not controlled
	Other endocrine diseases that are not controlled
	Considered inappropriate for the trial by the principal investigator

ALA-PDD. Hysteroscopic observation showed a white protruding lesion in the anterior wall of the lower uterine segment (Fig. 1A). The lesion was PDD-positive and suspected to be APA (Fig. 1B), and was removed hysteroscopically with margins. No other protruding lesion was found in the uterine cavity (Fig. 1C) and these areas were PDD-negative (Fig. 1D). Endometrial biopsy was performed in several of the PDD-negative areas using a hysteroscope. Histopathologically, APA lesion was found only in PDD-positive areas (Fig. 2A, B). There were no histopathological APA or malignant findings in specimens collected from PDD-negative areas. Endometrial tissue in each specimen was very little and it was difficult to determine the secretory phase and proliferative phase histopathologically. Specimens from the PDD-negative areas were histopathologically diagnosed as smooth muscle tissue. The patient was discharged from hospital on postoperative day (POD) 1 and is currently being followed up as an outpatient. She has had no recurrence for six months to date.

3. Discussion

No treatment protocols for APA have been established. The first-line treatment for patients who do not desire fertility preservation is total hysterectomy, whereas the options for patients requiring fertility preservation are surgical partial resection including hysteroscopic tumor resection and D&C, and hormone therapy with MPA. Matsumoto et al. reported a recurrence rate of 10% for APA after hysteroscopic tumor resection, which was better than that of 36.4% after D&C or vaginal resection [2]. However, Chiyoda et al. found a recurrence rate of 54.3% after initial hysteroscopic tumor resection [3]. Nomura et al. reported that 77.8% of patients with APA achieved a complete or partial response after treatment with MPA [1]; however, recurrence also occurred in 57.1% of patients with therapeutic effects [1]. Since the recurrence rate is high irrespective of the treatment method, a way to lower it should be considered. Our patient was treated with MPA after initial hysteroscopy for APA, but then required hysteroscopic tumor resection again for remaining APA. In our case, the lesion was easily identified using 5-ALA-PDD, and was consequently resected with sufficient margins. This is the first report of hysteroscopic tumor resection using 5-ALA-PDD in a patient with APA, and it is the first to show 5-ALA-PDD is likely to contribute to complete hysteroscopic resection APA lesion.

In a study of hysteroscopic ALA-PDD, Wyss et al. showed that endometrial cancer, endometrial hyperplasia and secretory endometrium were frequently PDD-positive [4]. Such PDD-positive tendency depends on that PpIX synthesis from 5-ALA accumulates in cells; however, the mechanism through which more PpIX accumulates in tumor cells compared to normal cells is not clear. PpIX accumulates in endometrial glands after intrauterine instillation of 5-ALA [5] and APA is a polypoidal tumor with a mix of atypical endometrial glands and smooth muscles, which raises the possibility that PpIX accumulation in gland cells led to the PDD-positive results. APA has low potential for malignant transformation, but a recent study has shown that APA can become malignant [6]. This suggests that atypical gland cells in APA may have molecular and cellular changes that are similar to those in malignant

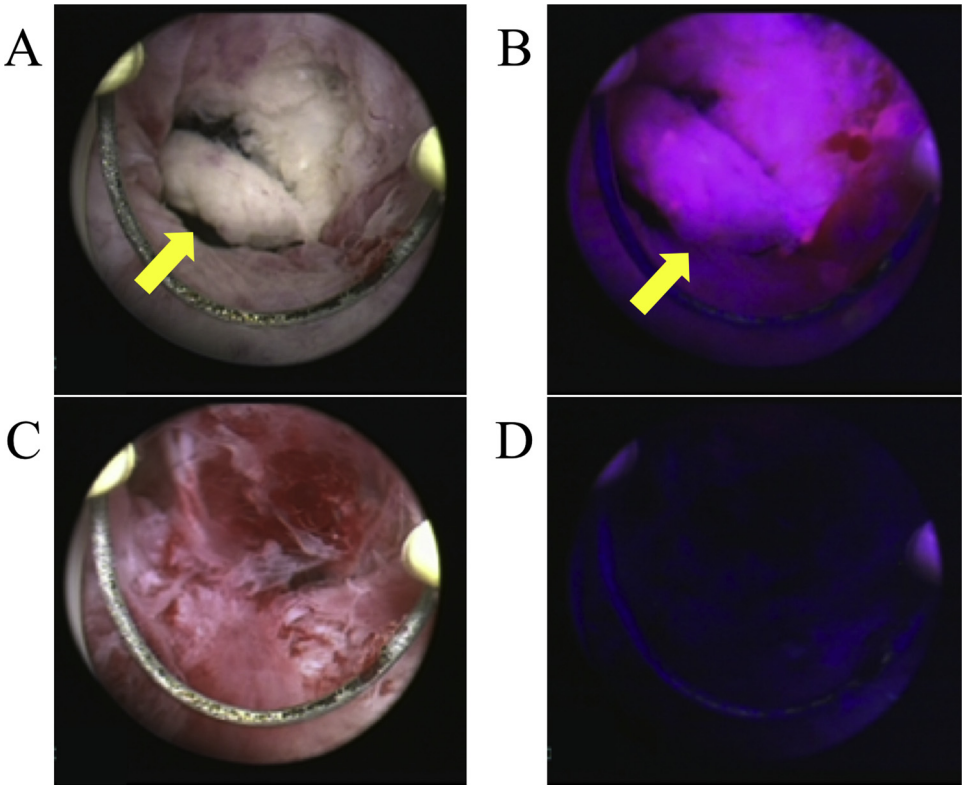

Fig. 1. Hysteroscopic findings. Lesion in the lower uterine body shown by white light (A) and by photodynamic diagnosis (PDD) (B). Lesion in the uterine cavity shown by white light (C) and by PDD (D). In the lower uterine body, a white protruding lesion was found (arrow) and recurrence of atypical polypoid adenomyoma was suspected. The lesion (arrow) under excitation light was PDD-positive, and was hysteroscopically removed with margins. No marked lesions were found in other areas of the uterine cavity and these areas were PDD-negative. Biopsy specimens were collected from several regions of the uterine cavity using a hysteroscope.

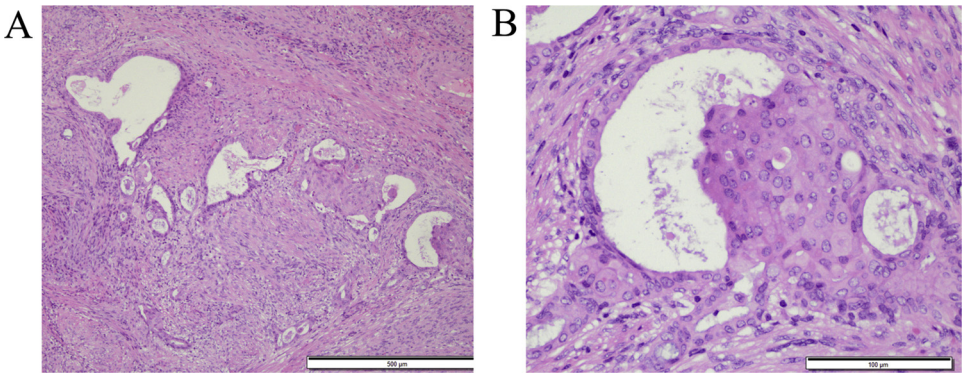

Fig. 2. Histopathological findings in hematoxylin-eosin staining. A white protruding lesion removed by hysteroscopy was visualized by hematoxylin-eosin staining. Atypical endometrial hyperplasia accompanied by nuclear enlargement and squamous metaplasia were found, with spindle cell hyperplasia in surrounding stromata. Based on these findings, the patient was diagnosed with atypical polypoid adenomyoma.

disease and are associated with PpIX accumulation. Further studies are needed to understand this mechanism in detail.

4. Conclusion

Hysteroscopic tumor resection using 5-ALA-PDD was performed in a patient with APA as a fertility preservation method. There was no case report that a patient with APA underwent hysteroscopic tumor resection using 5-ALA-PDD, and it is the first to show that PDD is positive for an APA lesion. PDD made it easy to identify the tumor and to resect lesions with sufficient margins. Although treatment protocols for fertility preservation have not been established for APA, new methods that improve total surgical resection may contribute to lower recurrence rate for this tumor.

Acknowledgement

This study was supported by a JFE (Japanese Foundation for Research and Promotion of Endoscopy) Grant 2018.

References

[1] H. Nomura, Y. Sugiyama, T. Tanigawa, M. Matoda, H. Kanao, E. Kondo, N. Takeshima, Long-term outcomes of fertility-sparing treatment of atypical polypoid adenomyoma with medroxyprogesterone acetate, Arch. Gynecol. Obstet. 293 (1) (2016) 177–181.
[2] T. Matsumoto, M. Hiura, T. Baba, O. Ishiko, T. Shiozawa, N. Yaegashi, H. Kobayashi, H. Yoshikawa, N. Kawamura, T. Kaku, Clinical management of atypical polypoid adenomyoma of the uterus. A clinicopathological review of 29 cases, Gynecol. Oncol. 129 (1) (2013) 54–57.
[3] T. Chiyoda, B.L. Lin, K. Saotome, S. Kiyokawa, S. Nakada, Hysteroscopic transcervical resection for atypical polypoid adenomyoma of the uterus: a valid, fertility-preserving option, J. Minim. Invasive Gynecol. 25 (1) (2018) 163–169 e1.
[4] P. Wyss, A. Degen, R. Caduff, R. Hornung, U. Haller, M. Fehr, Fluorescence hysteroscopy using 5-aminolevulinic: a descriptive study, Lasers Surg. Med. 33 (3) (2003) 209–212.
[5] M.K. Fehr, P. Wyss, B.J. Tromberg, T. Krasieva, P.J. DiSaia, F. Lin, Y. Tadir, Selective photosensitizer localization in the human endometrium after intrauterine application of 5-aminolevulinic acid, Am. J. Obstet. Gynecol. 175 (5) (1996) 1253–1259.
[6] Q.Y. Jiang, L. Wang, R.J. Wu, A multiple perspectives on atypical polypoid adenomyoma of uterus, Gynecol. Endocrinol. 29 (7) (2013) 623–625.