

Treatment of menorrhagia due to aplastic anemia by hysteroscopic resection of endometrial functional layer and levonorgestrel-releasing intra-uterine system

Three case reports

Huadi Yang, MD, Xuqun Xu, BD, Xuelu Jiang, BD, Zhitao Yao, MD*

Abstract

Rationale In women, menorrhagia associated with aplastic anemia (AA) is secondary to thrombocytopenia and can be acute and severe. Endometrial ablation or hysterectomy has been reported to achieve beneficial results. However, serious limitations and long-term complications exist. We report this clinical case series with the aim of sharing our experiences and exploring a safe and effective way to treat abnormal uterine bleeding (AUB) AA women with future fertility desire.

Patient concerns The 3 young patients aged 25 to 29 years old suffered from AUB secondary to AA.

Diagnosis They were diagnosed with AA by bone marrow biopsy and presented with symptoms and signs of AUB without other identified causations.

Interventions When the platelet count was between $30 \times 10^9/L \sim 50 \times 10^9/L$ after a blood transfusion, each patient received a hysteroscopic resection of endometrial functional layer and was fitted a levonorgestrel-releasing intra-uterine system (LNG-IUS) in uterine cavity following the surgery.

Outcomes All the patients recovered without incident and were discharged in clinically stable conditions.

Lessons In conclusion, AUB secondary to AA can be acute and severe. Hemostasis is more difficult due to progressive pancytopenia. For young women with future fertility desire, LNG-IUS following hysteroscopic resection of endometrial functional layer is a safe and effective way against endometrial ablation or hysterectomy.

Abbreviations: AA = aplastic anemia, AUB = abnormal uterine bleeding, LNG-IUS = levonorgestrel-releasing intra-uterine system.

Keywords: abnormal uterine bleeding, aplastic anemia, hysteroscopic resection of endometrial functional layer, levonorgestrel-releasing intra-uterine system

Editor: N/A.

HY and XX contributed equally to this work.

The patients discussed in this case series gave their full permission for the disclosure of their case histories, images, and textual materials for publication.

This case was not a clinical trial and no off-label drugs were used so, the ethical approval is not necessary for this case report.

There were no funding sources for this research.

The authors have no conflicts of interest to disclose.

Department of Gynecology and Obstetrics, Zhejiang Hospital of Traditional Chinese Medicine, Hangzhou, Zhejiang, China.

* Correspondence: Zhitao Yao, Zhejiang Hospital of Traditional Chinese Medicine, Hangzhou, Zhejiang China (e-mail: 22683406@qq.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:17(e15156)

Received: 20 October 2018 / Received in final form: 19 February 2019 / Accepted: 15 March 2019

<http://dx.doi.org/10.1097/MD.0000000000001516>

1. Introduction

Aplastic anemia (AA) is characterized by bone marrow failure and pancytopenia.^[1] In women, menorrhagia associated with AA is secondary to thrombocytopenia and can be acute and severe. Packed red blood cells and platelet transfusions support the patient clinically. However, it may take weeks or months to respond to definitive therapy as low hemoglobin and platelet persist due to uterine bleeding. Endometrial ablation or hysterectomy has been reported to achieve beneficial results for heavy abnormal uterine bleeding (AUB) in AA,^[2,3] but serious limitations and long-term complications exist,^[4] especially for young women with fertility requirements.

Over the past 2 years, we have used levonorgestrel-releasing intra-uterine system (LNG-IUS) to treat AUB young women with AA following hysteroscopic resection of endometrial functional layer and achieved significant results. We report these clinical cases with the aim of sharing our experiences and exploring the ways to treat AUB of young women with future fertility desire secondary to AA against endometrial ablation or hysterectomy.

Table 1
Patient materials and treatment.

Case/data	Age	Chief complaint	History of AA	Current treatment
Case 1	25	Heavy menstrual bleeding for the past 15 days, which had occurred intermittently for the past 2 years.	6 years	Taking testosterone undecanoate (TU) soft capsules 2 tablets each time twice a day orally
Case 2	27	Heavy menstrual bleeding for the past 10 days, which had occurred intermittently for the past 5 years.	5 years	Taking testosterone undecanoate (TU) soft capsules 2 tablets each time twice a day orally
Case 3	29	Heavy menstrual bleeding for the past 20 days, which had occurred intermittently for the past 1 year.	6 years	Taking testosterone intramuscular injection of 100 mg, every other day

2. Case series description

Patients were included in this study if they were diagnosed with AA by bone marrow biopsy and presented with symptoms and signs of AUB without other identified causations such as uterine fibroids, endometrial polyps, and cancer. All the patients had a desire for future fertility.

The treatment was performed after approval from the Medical Ethics Committee of The First Affiliated Hospital of Zhejiang Chinese Medical University. Before the treatment, all patients and their family were comprehensively counseled about the benefits of endometrial ablation or hysterectomy and the potential risks of LNG-IUS following hysteroscopic resection of endometrial functional layer and gave written informed consent. Especially for the virgin patient, she and her parents gave full consent to accept this treatment. At last, all the patients regarded this treatment as the most acceptable procedure.

All the patients completed a series of 10 units of platelets, 4 units of hemoglobin and intravenous antibiotics (meropenem) for prophylaxis infection before the surgery. The details of images, textual materials, and laboratory data for each case when they turned to the gynecological ward were summarized in Table 1 and Table 2.

2.1. Case 1

A 25-year-old woman was admitted to the gynecological ward, having shown symptoms of heavy menstrual bleeding with approximately 40 to 120 mL of blood loss every day for the past 15 days, which had occurred intermittently for the past 2 years. She had been diagnosed with AA for 6 years. And she had been taking testosterone undecanoate (TU) soft capsules with 2 tablets each time twice a day orally, which promoted hematopoiesis, to control her condition. Excessive bleeding and low hemoglobin rendered that she needs blood transfusion every other day. In addition, she was a virgin who denied history of sexual activity.

During the examination, she appeared to be pale but had a regular blood circulation (pulse 89/min and blood pressure 94/62 mm Hg). The pregnancy test was negative. Pelvic ultrasonography revealed the endometrial thickness (double layer) was 1.20 cm and

normal uterus and adnexal structure. The pertinent laboratory findings were as follows: hemoglobin: 46 g/L, platelets: $31 \times 10^9/L$, total leukocytes: $3.5 \times 10^9/L$, prothrombin time 12.20 s and activated partial prothrombin time 23.50 seconds.

After completing a blood transfusion and antibiotics for prophylaxis infection, surgery was performed after admission with $49 \times 10^9/L$ platelet count and 55 g/L hemoglobin. On hysteroscopic surgery, her intrauterine depth was 8.0 cm. Functional layer of endometrium was resected under the guidance of ultrasound, and the rollerball was used at the endometrium bleeding regions with a touch technique applying no pressure.^[5] The treatment endpoint was that there was no visible bleeding in the endometrium. Focal lesions were sent to the pathology laboratory. Importantly, intrauterine landmarks (tubal ostia, internal cervical os, and/or the characteristic appearance of the endometrium) were identified to confirm that the cavity had been entered and ensured that the operator had not created a false passage.^[5] At last, she was fitted an LNG-IUS in the uterus cavity. The time of surgery was less than 35 minutes and the intraoperative blood loss was less than 30 mL. She was transferred to the gynecological ward and received intravenous meropenem for infection prophylaxis and carbazochrome sodium sulfonate to stanch bleeding. Followed up for 6 months, She recovered very well without bleeding in the vagina since the surgery. Histopathological evaluation revealed irregular hyperplasia of the endometrium.

2.2. Case 2

A 27-year-old woman presented to the gynecological ward with complaints of heavy menstrual bleeding with approximately 80 to 140 mL of blood loss every day for the past 10 days, which had occurred intermittently for the past 5 years. She had been diagnosed with AA for 5 years. And she had also been taking testosterone undecanoate (TU) soft capsules with 2 tablets each time twice a day orally to control her condition. Further, she had taken ethinylestradiol and cyproterone acetate tablets (Diane-35) to control bleeding, but it made little difference. Because of excessive bleeding and low hemoglobin, she had got blood transfusion every day. And she was married but without a child.

Table 2
Patient laboratory data and image materials.

Case/data	Laboratory data				Pelvic ultrasonography				
	Hemoglobin (g/L)		Platelets ($\times 10^9/L$)		Total leukocytes ($\times 10^9/L$)	Prothrombin time (s)	Activated partial prothrombin time (s)	Endometrial thickness (double layer) (cm)	
Moved to gynaecological ward	After a blood transfusion	Moved to gynaecological ward	After a blood transfusion						
Case 1	46	55	31	49	3.5	12.20	23.50	1.20	
Case 2	43	63	20	44	6.5	11.00	23.40	0.85	
Case 3	47	59	27	35	2.0	11.7	22.50	0.78	

On physical examination she was found to be pale but had a regular blood circulation (pulse 78/min and blood pressure 92/62 mm Hg). The pregnancy test was negative. Pelvic ultrasonography revealed the endometrial thickness (double layer) was 0.85 cm and normal uterus and adnexal structure. The pertinent laboratory findings were as follows: hemoglobin: 43 g/L, platelets: $20 \times 10^9/L$, total leukocytes: $6.5 \times 10^9/L$, prothrombin time 11.00 seconds and activated partial prothrombin time 23.40 seconds.

After completing a blood transfusion and antibiotics for prophylaxis infection, surgery was performed after admission with $44 \times 10^9/L$ platelet count and 63 g/L hemoglobin. On hysteroscopic surgery, her intrauterine depth was 8.5 cm. The procedure was the same as Case 1.

At last, she was also fitted an LNG-IUS in the uterus cavity. She was transformed to the gynecological ward and received the same treatment as Case 1. Followed up for 6 months, she recovered well with small amount of bleeding in the vagina since the surgery. Histopathological evaluation revealed irregular hyperplasia of the endometrium.

2.3. Case 3

The third patient was a 29-year old woman, who presented to the gynecological ward due to the same symptoms of heavy menstrual bleeding with approximately 100 to 160 mL of blood loss every day for the past 20 days, which had occurred intermittently for the past 1 years. She had been diagnosed with AA for 6 years. And she had been taking testosterone intramuscular injection of 100 mg, every other day to control her condition. Taking Diane-35 made little difference to her either, and she had got blood transfusion every day. She had sexual activity ever and denied having sex for nearly 3 years.

On physical examination, she was found to be pale but had a regular blood circulation (pulse 80/min and blood pressure 90/64 mm Hg). The pregnancy test was negative. Pelvic ultrasonography revealed the endometrial thickness (double layer) was 0.78 cm and normal uterus and adnexal structure. The pertinent laboratory findings were as follows: hemoglobin: 47 g/L, platelets: $27 \times 10^9/L$, total leukocytes: $2.0 \times 10^9/L$, prothrombin time 11.70 seconds and activated partial prothrombin time 22.50 seconds.

After completing a blood transfusion and antibiotics for prophylaxis infection, surgery was performed after admission with $35 \times 10^9/L$ platelet count and 59 g/L hemoglobin. On hysteroscopic surgery, her intrauterine depth was 10.0 cm. The procedure was the same as Case 1.

At last, she was not fitted an LNG-IUS in the uterus cavity. She was transformed to the gynecological ward and received the same treatment as Case 1. Besides that, she took gonadotropin-releasing hormone agonist (GnRH-a) for 3 months to reduce the uterine bulk via ovulation suppression. 3 months later, her intrauterine depth was 8.5 cm and she was fitted an LNG-IUS as the other ones. Followed up for 6 months, she recovered well with small amount of bleeding in the vagina since the surgery. Histopathological evaluation revealed irregular hyperplasia of the endometrium.

3. Discussion

AA is a rare disorder characterized by suppression of bone marrow function resulting in progressive pancytopenia.^[1] Anemia, hemorrhage, and infection are the typical symptoms of patients with AA but generally, there is no long-standing

illness.^[1] Initial manifestations range from generalized bleeding to weakness, fatigue, infection, and other manifestations of impaired tissue oxygenation including angina pectoris. Spontaneous hemorrhage can occur when platelet levels are lower than $20,000/\mu L$.^[6] AUB secondary to AA can be acute and severe. Hemostasis is more difficult due to progressive pancytopenia. And the use of testosterone to control AA condition makes Diane-35 less effective.

Endometrial ablation is appropriate for treatment of nonmalignant AUB in premenopausal women who do not desire future fertility. While the first peak of incidence age to women with AA is 20 to 24 years old.^[7] Women of this age usually have a potential for future pregnancy. Besides, up to 20% of women reported pain following endometrial ablation.^[5] And also, endometrial cancer is another serious concern with endometrial ablation because endometrial specimens cannot be obtained during the surgery.

It was reported that hysterectomy should be considered the preferred strategy for the treatment of AUB based on cost-effectiveness.^[8] However, the low platelet count secondary to AA makes the surgery risky and potentially fatal, and a significant number of women with AUB are keen to preserve their uterus.^[9]

The potential for future pregnancy makes endometrial ablation or hysterectomy unsuitable for young women. Neither was endometrial curettage, because bleeding after this surgery may be continual and severe secondary to low platelet. LNG-IUS following hysteroscopic resection of endometrial functional layer was confirmed to be effective and safe in our cases. We achieved beneficial results by resecting the functional layer of endometrium and stanching bleeding regions under the direct vision of hysteroscopy. The local release of levonorgestrel by an LNG-IUS in the uterine cavity suppressed endometrial growth and reduced menstrual bleeding effectively.^[10] In the Society of Gynecologists and Obstetricians of Canada (SOGC) guideline on AUB, the use of the LNG-IUS is a simple treatment option and is more cost-effective than any surgical technique.^[11] Moreover, LNG-IUS following hysteroscopic resection of endometrial functional layer in this work resulted in short duration of surgery, short hospital stay, and quick recovery time. The patient was satisfied with the treatment results. Without the trouble of AUB, both their hemoglobin and quality of life have reached a higher level. Further multicentre and prospective large-sample randomized controlled trials are required before this modality can be widely used in gynecology and hematology field.

Author contributions

Conceptualization: Huadi Yang, Zhitao Yao.

Data curation: Huadi Yang, Xuqun Xu, Xuelu Jiang.

Formal analysis: Huadi Yang, Xuqun Xu, Xuelu Jiang.

Writing – review & editing: Huadi Yang, Xuqun Xu, Zhitao Yao. Huadi Yang orcid: 0000-0002-9151-3332.

References

- [1] Peslak SA, Olson T, Babushok DV. The diagnosis and treatment of aplastic anemia: a review. *Curr Treat Options Oncol* 2017;18:70.
- [2] Kim N, Donohue T, Sloand E, et al. Successful use of balloon ablation to treat menorrhagia complicating aplastic anemia. *Gynecol Obstet Invest* 2008;66:123–6.
- [3] Jacob S, Abdullah A, Hurwitz J, et al. Endometrial ablation for aplastic anemia-associated menorrhagia. *Conn Med* 2015;79:289–90.
- [4] Michelle Louie , Kelly Wrightb , Matthew Siedhof . The case against endometrial ablation for treatment of heavy menstrual bleeding. *Minim Invasive Gynecol Proced* 2018;37:1–6.

- [5] Laberge P, Leyland N, Murji A, et al. Endometrial ablation in the management of abnormal uterine bleeding. *April Jgoc Avril* 2015;322:366.
- [6] Hocking WG. Aplastic anemia in: Mazza JJ, eds. *Manual of Clinical Hematology*. 2002:61–73.
- [7] Chen J-B, Shao Z-H, Chu Y-L. Epidemiological study on aplastic anemia. *Chin J Hematol* 1999;4:
- [8] Roberts TE, Tsourapas A, Middleton LJ, et al. Hysterectomy, endometrial ablation, and levonorgestrel releasing intrauterine system (mirena) for treatment of heavy menstrual bleeding: cost effectiveness analysis. *BMJ* 2011;342:
- [9] Lethaby AE, Cooke I, Rees M. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2005;4:CD002126.
- [10] Shumarjav U, Kotani K, Taniguchi N. Association between serum C-reactive protein and metabolic syndrome in mongolian patients in comparison to Japanese patients. *Ethn Dis* 2011;21: 74–8.
- [11] Society of Gynecologists and Obstetricians of Canada (SOGC). Endometrial Ablation in the Management of Abnormal Uterine Bleeding. *APRIL JOGC AVRIL* 2015: 364.