Am J Transl Res 2021;13(10):12016-12020
www.ajtr.org /ISSN:1943-8141/AJTR0136245

Case Report

Heavy menstrual bleeding due to primary myelofibrosis in a woman: a case report

Hui Li, Chao Li, Xinhe Shi, Mengting Xia

Department of Gynaecology and Obstetrics, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, Zhejiang Province, China

Received June 10, 2021; Accepted August 10, 2021; Epub October 15, 2021; Published October 30, 2021

Abstract: Heavy menstrual bleeding (HMB) due to primary myelofibrosis (PMF) is secondary to progressive pancytopenia, which is a rare and difficult to treat condition. We report this case with the aim of sharing our experiences and exploring a safe and effective way to treat patients with HMB due to PMF. A 40-year-old woman who had been taking combined oral contraceptives (COCs) for eight years was admitted to our hospital with HMB. A bone marrow biopsy report and genetic testing confirmed the diagnosis of PMF. Norethisterone tablets had an unsatisfactory hemostatic effect. The patient underwent a hysteroscopy and the insertion of a levonorgestrel intrauterine system (LNG-IUS). At the 5-month follow-up, the patient had a lower menstruation bleeding volume. COCs are unsuitable for managing the menstruation of patients with PMF in the long run. Endometrial ablation is the long-term method. However, the patient's fertility requirements should be taken into account. The insertion of an LNG-IUS after hysteroscopic curettage to exclude endometrial malignant lesions is recommended.

Keywords: COCs, endometrial ablation, heavy menstrual bleeding, LNG-IUS, primary myelofibrosis

Introduction

Primary myelofibrosis (PMF) is a bone marrow proliferative tumor caused by the clonal proliferation of hematopoietic stem cells, with an unknown origin and a hidden onset. The clinical manifestations of PMF mainly include progressive hemocytopenia, fever, and other systemic symptoms. With the progression of the disease, patients with advanced PMF often suffer from various types of bleeding and many patients eventually die of complications such as infections and bleeding caused by hemopenia. Allogeneic hematopoietic stem cell transplantation is currently the only way to cure PMF [1]. However, it may lead to blood transfusion dependence, iron overload, cachexia, in addition to its high treatment cost. Therefore, the median survival time (MST) of PMF was significantly reduced compared with other myeloid proliferative tumor diseases [2]. Menstruation disrupts blood vessels, the restoration of which requires an intact hemostatic system and the successful interaction of platelets, clotting factors, and fibrinolytic proteins [3]. Heavy menstrual bleeding (HMB), which was recently described as increased menstrual volume regardless of regularity, frequency, or duration by the Federation of Gynecology and Obstetrics (FIGO) in 2011 [4], can increase the susceptibility to iron deficiency, and if left untreated, it may progress to iron deficiency anemia, thus progressing and worsening PMF [5]. Therefore, each menstrual cycle is extremely risky and sometimes even fatal for women with PMF. Heavy menstrual bleeding caused by PMF is very rare. To our knowledge, this case has not been reported yet. Here, we report a case of heavy menstrual bleeding due to PMF with the aim of sharing our experiences and exploring a safe and effective way to treat these patients, and a literature review was performed.

Case report

The patient signed the informed consent and passed the examination with the approval of the ethics committee in our hospital (No. 2021-4108). A 40-year-old female, G3P1, was admitted to our hospital due to HMB, with dizziness

Table 1. The follow-up data from the routine blood tests

Date	Leukocyte (10^9/L)	Hemoglobin (g/L)	Platelet (10^9/L)	Note
Feb, 24, 2020	15.6	41	21	Morning
Feb, 24, 2020	20.4	53	14	Afternoon
Feb, 25, 2020	15.9	52	74	After a platelet transfusion
Feb, 26, 2020	20.4	45	27	-
Feb, 27, 2020	12	48	51	After a platelet transfusion
Mar, 01, 2020	16.2	80	57	After a platelet transfusion

Table 2. The follow-up data of the blood coagulation function

Date	PT (s)	APTT (s)	D-dimer (mg/L)	Note
Feb, 24, 2020	13.6	20.0	1.22	
Feb, 25, 2020	12.9	29.9	2.97	After a platelet transfusion
Feb, 27, 2020	11.5	27.2	16.24	Before Surgery
Mar, 01, 2020	11.4	25.9	9.1	

Note: PT: Prothrombin time; APTT: Activated partial prothrombin time.

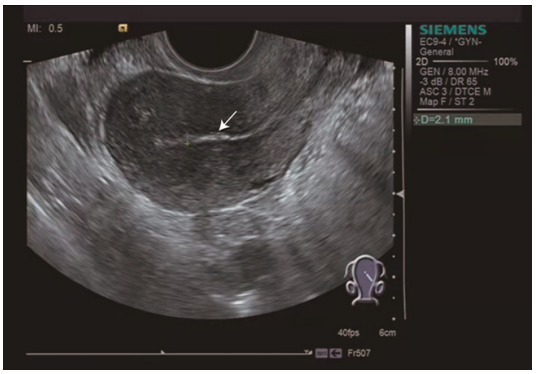

Figure 1. An ultrasound showing the normal size of the uterus and the thickness of the endometrial monolayer, which was about 0.21 cm (↑).

and palpitations on February 23, 2020. She had increased menstrual bleeding since her first period when she was 14 years old. She had not received any treatment until her cesarean section in 2003 when she was diagnosed with progressive thrombocytopenia. She refused to do a bone marrow biopsy and began to take combined oral contraceptives (Marvelon) periodically in 2012 to decrease her menstrual blood volume. Two days after the routine withdrawal of Marvelon, the patient had her last period on February 18, 2020, with a large amount of blood clots. She denied a history of other major illnesses and her previous ultrasound showed no uterine polyps, adenomyosis, or uterine leiomyomas. A gynecological examination indicated that the vagina was filled with blood and there were no neoplasms on the cervix, and the uterus was of normal size. A blood examination indicated a leukocyte count of 16.8×10^9/L, an erythrocyte count of 2.32×10^{12}/L, a hemoglobin count of 61 g/L, a platelet count of 27×10^9/L, a neutrophil percentage of 72%, a neutrophil absolute number of 12.0×10^9/L, a lymphocyte absolute value of 3.9×10^9/L, a red blood cell distribution width (RDW) of 19.8%, and a C-reactive protein (CRP) level of 6.21 mg/L. The platelet count decreased gradually after admission (**Table 1**). Manual classification of white blood cells: 85% of neutrophils and 11% of lymphocytes. The prothrombin time was 13.60 seconds, fibrinogen 1.29 g/L, the thrombin time was 17.20 seconds, the partial thrombin activity time was 20.00 seconds, and the D-dimer was 1.22 mg/L fibrinogen equivalent units (FEU). Furthermore, as time went by, the D-dimer level was increasing gradually (**Table 2**). The follicle stimulating hormone (FSH) level was 0.19 IU/L, the luteinizing hormone (LH) level was 0.08 IU/L, the prolactin was 426.59 mIU/L, the estradiol level was 61.22 pmol/L, and the progesterone level was 2.77 nmol/L. Her tumor markers, liver and kidney functions, and her serum ferritin, folic acid, and vitamin B12 levels were normal. The ultrasound indicated her spleen and uterus were of normal size, and the thickness of her endometrial monolayer was about 0.21 cm (**Figure 1**).

The dry drainage phenomenon was found in a bone marrow puncture three times in this patient. Her bone marrow routine indicated low nuclear cell proliferation (**Figure 2A**). A bone marrow biopsy pathology showed the ratio of her bone marrow hematopoiesis: the fat was about 65%:35%, with an active proliferation of the karyocytes and granulocytes, and the karyocytes in the mature stage were dominant. The erythrocyte hyperplasia was less active, and the hyperplasia of the middle and late red

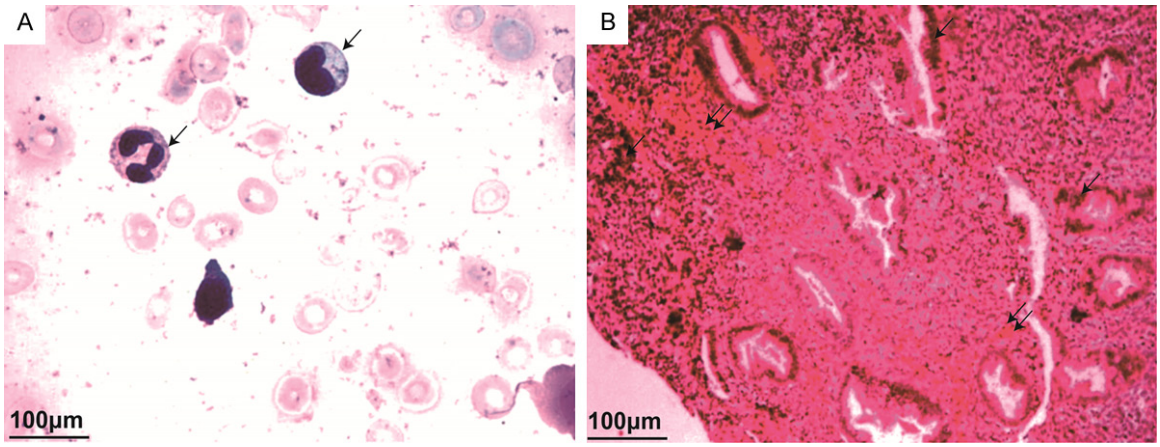

Figure 2. Bone marrow staining. A: Bone marrow routine indicating low nuclear cell proliferation (↑) (×400). B: The pathological section showing the active proliferation of karyocytes and granulocytes (↑), and the karyocytes in the mature stage were dominant. The erythrocyte hyperplasia was less active (↑↑), and the hyperplasia of middle and late red blood cells was dominant (×100).

blood cells was dominant. There were 1-7 megakaryocytes/HPF (high power field), as well as naked nuclei and small nuclei megakaryocytes, with a few mature lymphocytes. Special staining results indicated reticular fiber (++), Perls (-) (**Figure 2B**). A gene detection report showed no mutations in the 10 types of gene point mutations related to myelodysplastic syndromes (MDS), namely tet methylcytosine dioxygenase 2 (TET2) exon 3-11, DNA nucleotide methyltransferase 3A (DNMT3A) R882, tumor protein P53 (TP53) exon 2-11 additional sex combs like 1 (ASXL1), splicing factor 3b subunit 1 (SF3B1) exon 14-16, serine and arginine rich splicing factor 2 (SRSF2), U2 small nuclear RNA auxiliary factor 1 (U2AF1) exon 2/6, runt-related transcription factor 1 (RUNX1) exon 3-8, enhancer of zeste homolog 2 (EZH2) exon 16-20, neuroblastoma RAS viral oncogene homolog (NRAS) exon 2/3. No mutation was detected in the gene points mutations related to the myeloproliferative neoplasms, namely Janus kinase 2 (JAK2) 14exon, JAK2 12exon, myeloproliferative leukemia virus oncogene (MPL) 10exon and Calreticulin (CALR) 9exon. The breakpoint cluster region-Abelson (BCR-ABL) P230 fusion gene was negative. The hematologist was consulted, and the patient was diagnosed with primary myelofibrosis (PMF).

Treatments include doxytocin 20 U via intravenous drip daily and norethindrone tablets orally 5 mg every eight hours. Meanwhile, homologous erythrocytes, platelets and plasma transfusions were performed after explaining the patient's condition and receiving the consent of the patient and her family. After three days of the treatment, the patient's menstrual blood volume showed no significant reduction. Therefore, after a platelet transfusion hysteroscopy and a diagnostic curettage were performed on February 27, 2020, the procedures revealed that the endometrial thickness was normal and there was no neoplasm in the uterine cavity. The postoperative pathology examination indicated that the endometrial glands were in the secretory stage and the stroma had an anterior decidual change. Subsequently, a levonorgestrel releasing intrauterine system (LNG-IUS) was inserted in the uterus on March 1, 2020. During the follow-up for five months, the patient's menstrual blood volume decreased gradually and currently she has regular periods with less menstrual bleeding.

Discussion

HMB is acute and fatal. High-quality evidence demonstrates that about 13% of women with HMB have biochemically detectable systemic hemostatic disorders [6]. The patient in this case was finally diagnosed with PMF through a bone marrow biopsy and a genetic test after her admission. According to the PLAM-COINE naming system (P: polyp, L: leiomyoma, A: adenomyosis, M: malignancy and hyperplasia, C: coagulopathy, O: ovulatory dysfunction, I: iatrogenic: N: not yet classified, E: endometrial) pub-

lished by FIGO in 2011, the patient was in the category of AUB-C (abnormal uterine bleeding-coagulopathy). The preferred treatment of AUB-C is atrophying endometrium with a high dose of high efficiency synthetic progesterone [7]. Therefore, based on the symptomatic treatment with platelet transfusion and the correction of the anemia, the patient was given norethisterone tablets 5 mg every eight hours after admission. However, the peculiarity of this case is that the norethindrone tablets were not ideal for the hemostatic effect in this patient. We considered that it might be related to the long-term use of combined oral contraceptives (COCs) before the patient's admission.

COCs are a common method for the clinical treatment of abnormal uterine bleeding (AUB) [8]. The mechanism of COCs is to inhibit the secretion of FSH and LH by the negative feedback of high efficiency synthetic estrogen and progesterone in COCs, thus inhibiting the secretion of endogenous estrogen and progesterone from the ovary. It has been reported that long-term use of COCs can over-inhibit the hypothalamic-pituitary-ovarian (H-P-O) axis and thus inhibit endometrial growth [9]. The hemostatic effect mechanism of the norethisterone tablets is to transform the endometrium in the proliferative phase into the secretory phase. In this case, the patient was taking COCs for eight years, and the endometrial thickness of the patient at admission was only 0.21 cm per layer. Therefore, the norethisterone tablets had no effect on this patient.

Endometrial ablation is also a common treatment for HMB. But long-term complications exist. Patients can develop local hematometra which may lead to rebleeding, infection, and pelvic pain. Besides, endometrial cancer is another serious concern with endometrial ablation because endometrial specimens cannot be obtained during the surgery [10]. Under this condition, we think it is better to perform hysteroscopic curettage to exclude endometrial malignant lesions and then insert the levonorgestrel releasing intrauterine system into the uterine cavity.

The levonorgestrel releasing intrauterine system (LNG-IUS), which can release 20 ug levonorgestrel stably every day, was originally developed for use as an effective and reversible contraceptive. However, there is increasing evidence for its effectiveness in treating menorrhagia, and it is commonly used to manage women who would have previously resorted to surgical treatments [11]. The major mechanism of action of the LNG-IUS is through its local suppressive effect on the endometrium, including glandular atrophy and the decidualization of the stroma [12]. Approximately 20% of LNG-IUS users experience amenorrhea during at least one 90-day interval by the first year after insertion [13]. This kind of "amenorrhea" is not caused by impaired ovarian function or damaging endometrium. Therefore, LNG-IUS provides a better choice to patients who may have fertility requirements in the future than COCs or endometrial ablation. In addition, compared with COCs, the LNG-IUS does not harm the functions of other organs, as it only acts locally on the endometrium [14]. This makes LNG-IUS safer for patients with hematological diseases.

Conclusion

PMF is a progressive disease. In order to prevent HMB from occurring, gynecologists need to assist in the management of menstruation in patients with PMF at an early stage. COCs are not suitable for managing menstruation in the long run, and endometrial ablation is not recommended for patients who have fertility requirements. Compared with COCs and endometrial ablation, the insertion of LNG-IUS into the uterine cavity after hysteroscopic curettage to exclude endometrial malignant lesions is a safer and more effective long-term option.

Disclosure of conflict of interest

None.

Address correspondence to: Mengting Xia, Department of Gynaecology and Obstetrics, The First Affiliated Hospital of Zhejiang Chinese Medical University, No. 54 Youdian Road, Hangzhou 310006, Zhejiang Province, China. Tel: +86-0571-87070921; Fax: +86-0571-87070921; E-mail: xiamengting_tcm54@163.com

References

[1] Asher S, McLornan DP and Harrison CN. Current and future therapies for myelofibrosis. Blood Rev 2020; 42: 100715.

[2] Tefferi A. Primary myelofibrosis: 2021 update on diagnosis, risk-stratification and management. Am J Hematol 2021; 96: 145-162.

[3] Presky KO and Kadir RA. Women with inherited bleeding disorders-challenges and strategies for improved care. Thromb Res 2020; 196: 569-578.
[4] Beelen P, van den Brink MJ, Herman MC, Geomini PMAJ, Dekker JH, Duijnhoven RG, Mak N, van Meurs HS, Coppus SF, van der Steeg JW, Eising HP, Massop-Helmink DS, Klinkert ER, Nieboer TE, Timmermans A, van der Voet LF, Veersema S, Smeets NAC, Schutte JM, van Baal M, Bossuyt PM, Mol BWJ, Berger MY and Bongers MY. Levonorgestrel-releasing intrauterine system versus endometrial ablation for heavy menstrual bleeding. Am J Obstet Gynecol 2021; 224: 187.e181-187.e110.
[5] Wang W, Bourgeois T, Klima J, Berlan ED, Fischer AN and O'Brien SH. Iron deficiency and fatigue in adolescent females with heavy menstrual bleeding. Haemophilia 2013; 19: 225-230.
[6] Munro MG, Critchley HOD and Fraser IS; FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynaecol Obstet 2018; 143: 393-408.
[7] Davis E and Sparzak PB. Abnormal uterine bleeding. Treasure Island (FL): StatPearls 2021.
[8] Amiri M, Nahidi F, Yarandi RB, Khalili D, Tohidi M and Tehrani FR. Effects of oral contraceptives on the quality of life of women with polycystic ovary syndrome: a crossover randomized controlled trial. Health Qual Life Outcomes 2020; 18: 293.
[9] Chen KX, Worley S, Foster H, Edasery D, Roknsharifi S, Ifrah C and Lipton ML. Oral contraceptive use is associated with smaller hypothalamic and pituitary gland volumes in healthy women: a structural MRI study. PLoS One 2021; 16: e0249482.
[10] Louie M, Wright K and Siedhoff MT. The case against endometrial ablation for treatment of heavy menstrual bleeding. Curr Opin Obstet Gynecol 2018; 30: 287-292.
[11] Kingman CE, Kadir RA, Lee CA and Economides DL. The use of levonorgestrel-releasing intrauterine system for treatment of menorrhagia in women with inherited bleeding disorders. BJOG 2004; 111: 1425-1428.
[12] Mittermeier T, Farrant C and Wise MR. Levonorgestrel-releasing intrauterine system for endometrial hyperplasia. Cochrane Database Syst Rev 2020; 9: CD012658.
[13] Sergison JE, Maldonado LY, Gao X and Hubacher D. Levonorgestrel intrauterine system associated amenorrhea: a systematic review and metaanalysis. Am J Obstet Gynecol 2019; 220: 440-448, e448.
[14] Zakhari A, Delpero E, McKeown S, Tomlinson G, Bougie O and Murji A. Endometriosis recurrence following post-operative hormonal suppression: a systematic review and meta-analysis. Hum Reprod Update 2021; 27: 96-107.