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Challenges in Managing AUB-C in Adolescence with Acute Lymphoblastic Leukemia in North Sumatera, Indonesia: A Case Report

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Abstract

BACKGROUND: Abnormal uterine bleeding is a common problem not only cause health disturbance but also affect the physical, social, emotional status, and quality of life of a women. The most common symptom is abnormally heavy or prolonged uterus bleeding. FIGO introduces nine categories cause of abnormal uterine bleeding, which are known as "PALM-COEIN." In general, components in "PALM" are components of structural abnormality, which can be diagnosed by imaging and/or histopathological examination, while "COEIN" includes non-structural abnormality.

CASE REPORT: A 17-year-old female without a history of sexual intercourse came to the gynecology polyclinic of the University Of North Sumatra hospital with a chief complaint of irregular menstruation that had been experienced by the patient since 5 months ago. The patient claimed to have had menstruation for 10−14 days, 4−5 times changing pads. Gynecology examination was within normal limits. Blood analysis has been done 3 times and the results came up with a significant decrease of platelet counts and hemoglobin levels.

Transabdomen ultrasonography was done and showed no abnormality found. The patient was diagnosed with AUB-C in acute lymphoblastic leukemia.

CONCLUSION: Abnormal uterine bleeding (AUB) is a common finding in women during their reproductive years. There are steps on how to diagnose an abnormal uterine bleeding disorder (AUB) based on comprehensive history taking, followed by a physical and additional workup.

Introduction

Abnormal uterine bleeding (AUB) is a common problem in age-reproductive women worldwide. The prevalence of abnormal uterine bleeding in an age-reproductive woman is 3−30%. About one-third of all women in the world had AUB throughout their life [1]. In an age-reproductive woman, the incidence of abnormal uterine bleeding is approximately 14−25%. The result of AUB not only can cause health disturbance but also affect the physical, social, emotional status, and quality of life of a women [2], [3]. The most common symptom is menorrhagia defined as abnormally heavy or prolonged uterus bleeding, in which the cause has not been identified [4].

The etiologies of AUB are caused by multifactorial including anatomic abnormalities, hormonal dysfunction, infections, systemic diseases, and complications due to pregnancy. Therefore, AUB can occur in women of all ages. However, the incidence of abnormal uterine bleeding is more often found in women of reproductive age [5]. FIGO introduces nine categories of causes of abnormal uterine bleeding, which are known as "PALM-COEIN," including: polyps, adenomyosis; leiomyoma; malignancy, and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; and iatrogenic; not yet classified. In general, components in "PALM" are components of structural abnormality, which can be diagnosed by imaging and/or histopathological examination, while "COEIN" includes non-structural abnormality [1], [3].

A cross-sectional study was conducted in Chinato evaluating the prevalence of etiologies of AUB in Beijing Shijitan Hospital, Capital Medical University. The classification of AUB by FIGO (2011) was used in the evaluation and obtained from a total of 1053 participants, AUB due to ovulatory dysfunction was the most common etiologies, which was around 57.7%. Furthermore, AUB due to polyps is around 16.2%, AUB due to leiomyoma is around 12%, AUB due to adenomyosis is around 4.94%, AUB due to endometrial

Table 1: Definition of normal and abnormal menstrual bleeding [8]

Menstrual cycle terms	Descriptive terms	Definition
Frequency (interval between the start of each menstrual cycle)	Infrequent	> 38 days
	Normal	24 to 38 days
	Frequent	< 24 days
Regularity (variation of menstrual cycle length, measured over 12 months)	Regular	+ 2 to 20 days over 12 months
	Irregular	> 20 days over 12 months
Duration of menstruation	Shortened	<4.5 days
	Normal	4.5 to 8 days
	Prolonged	> 8 days
Volume (total blood loss each menstrual cycle)	Light	< 5 mL
	Normal	5 to 80 mL
	Heavy	> 80 mL
Other terms	Amenorrhea	No bleeding for 90 days
	Primary amenorrhea	Absent menarche by 15 years of age
	Secondary amenorrhea	Amenorrhea for 6 months with previously regular menstrual cycles
	Menopause	Amenorrhea for 12 months without other apparent cause
	Precocious menstruation	Menarche before 9 years of age

disorders is about 2%, AUB due to iatrogenic about 2%, AUB due to malignancy is around 1.9%, and AUB with no apparent causes, about 0.9% [6].

Case Presentation

Ms, W. 17 years old, Virgo, Karo ethnicity, Islam, a high school student, came to the gynecology polyclinic of the University of North Sumatra Hospital on June 14, 2022, with the main complaint of irregular menstruation since 5 months ago. The patient claimed to have had menstruation for 10−14 days, 4−5 times changing pads. History of frequent large bruises from minor bumps or injuries was found, history of frequent bleeding from gums was found, history of epitaxis was found, history of abdominal pain was not found, and history of enlarged abdomen was not found. History of weight loss and appetite was found, 15 kg in 9 months. There was history of chemotherapy, six cycles for acute lymphocytic leukemia. History of taking herbs was not found. History of vaginal discharge was not found. Urination and defecation are within normal limits.

The patient had menarche at 12 years old, with a 28-day cycle, and regular within 3−5 days. The patient regularly changed 2 to 3 times pad in a day with history of dysmenorrhea.

On physical examination, the patient's weight is 46 kg, height 150 cm, and body mass index 20,4 kg/m^2. Vital signs were found, blood pressure 119/75 mmHg, pulse 80x/I, breath 20x/minute, and temperature 36.7°C. The obstetrics examination was within normal limits.

On rectal examination, the uterus was anteflexed, normal size, no palpable mass, and right and left adnexa which were not palpable, and both parametrium ware laxed. Douglas cavity was not protruded, Sphincter ani was tight, ampula recti was empty, with no blood on the site.

The patient was investigated for routine hematological and sonographic findings. Blood analysis has been done on June 14, 2022, June 16, 2022, and June 20, 2022, with significant platelet decrease with 13.000/uL, 8.000/uL, and 52.000/uL (normal limit: 150. 000−400.000/uL) and significant decrease of hemoglobin (Hb) with 10.8 g/dL, 5.8 g/dL, and 6.0 g/dl. Normal MCV, MCH, and MCHC suggest normocytic normochromic anemia. Leukocyte is significantly decreased with 1.020/uL, 370/ul, and 4.040/uL.

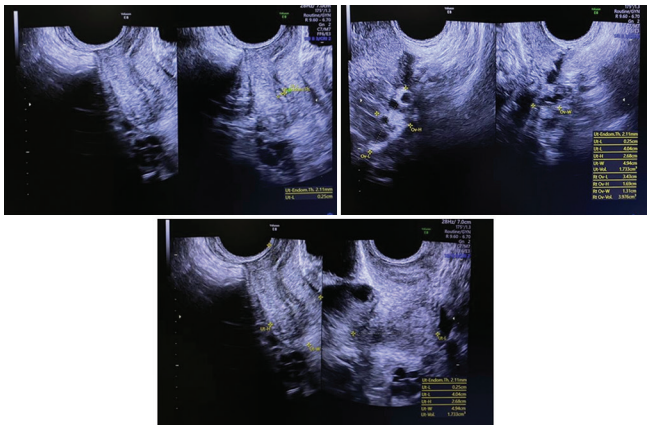

Figure 1: Transabdomen ultrasonography on June 14, 2022

Transabdomen ultrasonography on June 14, 2022 shows gynecology within the normal limit which was found. The patient was diagnosed with AUB-C in acute lymphoblastic leukemia (Figure 1).

Discussion

The International Federation of Gynecology and Obstetrics (FIGO) recommends the use of the term abnormal uterine bleeding (AUB) to describe any abnormality in the volume, regularity, duration, and/or frequency of menstruation in non-pregnant women (Table 1).

Abnormal uterine bleeding is considered chronic if it has been present for approximately 6 months, or acute when an episode of heavy bleeding requires immediate intervention. Abnormal uterine bleeding impacts the physical, emotional, and sexual aspects of a woman's life and can worsen a woman's quality of life [1], [7].

In this patient, the duration of menstruation is categorized as prolonged duration. The uterine and ovarian arteries supply blood to the uterus. This artery becomes the arcuate artery; the arcuate artery, then, sends out radial branches that supply blood to the two layers of the endometrium, the functional and the basal layers. Progesterone levels drop at the end of the menstrual cycle, causing the enzymatic breakdown of the functional

lining of the endometrium. This damage causes blood loss and sloughing, which leads to menstruation. Platelets, thrombin, and endometrial arterial vasoconstriction control blood loss. Any abnormalities in the structure of the uterus (such as leiomyomas, polyps, adenomyosis, malignancy, or hyperplasia), abnormalities in the clotting pathway (coagulopathy or iatrogenic), or disturbances of the hypothalamic-pituitary-ovarian axis (through ovulatory/ endocrine or iatrogenic disorders) can affect menstruation and causes abnormal uterine bleeding [9].

A system of classification and terminology for the etiology of AUC symptoms has been arranged by FIGO. By this system, the etiology of AUB is classified as "associated with structural abnormalities of the uterus" and "not associated with structural abnormalities of the uterus" and is categorized according to the PALM-COEIN acronym: Polyps, Adenomyosis, Leiomyoma, Malignancy, and hyperplasia, Coagulopathy, Ovulation dysfunction, Endometrial, Iatrogenic, and has not been classified [10].

Polyp (AUB-P)

Polyps are an epithelial proliferation consisting of vascular, glandular, fibromuscular, and connective tissue components that vary. The prevalence of endometrial polyps ranges from 8% to 35%, and the incidence increases with age. Intermenstrual bleeding is the most common symptom, but many cases of polyps are asymptomatic [11].

Adenomyosis (AUB-A)

The presence of endometrial tissue in the myometrium is known as adenomyosis. The estimated prevalence of adenomyosis is varied, ranging from 5% to 70%. Many patients are asymptomatic, but those with symptoms usually complain of painful, heavy, or prolonged menstrual bleeding. On examination, a firm and enlarged uterus can be seen [11].

Leiomyoma (AUB-L)

Benign fibromuscular tumors of the myometrium are known by several names, including "leiomyoma," "myoma," and "fibroid." The prevalence of these lesions ranges from up to 70% in Caucasians and up to 80% in African women. Bleeding is a common symptom and usually presents as heavy or prolonged menstruation. The patient may report pain or pressure in the pelvis, and on examination, the uterus and abdomen may be enlarged or irregularly contoured [11].

Malignancy and hyperplasia (AUB- M)

Abnormal uterine bleeding is the most common symptom of endometrial cancer. Long-term exposure to estrogen is a major risk factor [12].

Coagulopathy (AUB-C)

The term "coagulopathy" covers the spectrum of systemic hemostatic disorders that may be associated with AUB. Research shows that about 13% of women with heavy menstrual bleeding have a biochemically detectable systemic hemostatic disorder, most commonly von Willebrand's disease [11].

Ovulatory dysfunction (AUB-O)

Ovulatory dysfunction can contribute to AUB, the symptom may consist of a combination of unpredictable bleeding times and variable flow rates, which, in some cases, leads to heavy menstrual bleeding. Although most ovulatory disorders have no known etiology, many also have an endocrinopathy (e.g., polycystic ovary syndrome, hypothyroidism, hyperprolactinemia, mental stress, obesity, anorexia, weight loss, or extreme sports such as those associated with athletic training) [11].

Endometrium (AUB-E)

AUB occurring in the context of a structurally normal uterus with regular menstrual cycles without evidence of coagulopathy most likely has an underlying endometrial cause [11].

Iatrogenic (AUB-I)

Various medical treatments can trigger abnormal uterine bleeding. Hormonal contraceptives are the most common cause of iatrogenic uterine bleeding (i.e., breakthrough bleeding) [11].

Not yet classified (AUB-N)

This category includes conditions that are poorly understood, rare disorders (e.g., arteriovenous malformations, myometrial hyperplasia, and endometritis), and conditions that do not fit into the classification system, such as cesarean scar defects [11].

In general, the components of the PALM group are commonly for structural entities that can be measured visually by imaging and/or histopathology techniques, whereas the COEIN group is associated with entities that are not defined by imaging or histopathology (non-structural) [1].

In this patient, imaging has been done by transabdominal ultrasound with normal interpretation. From this interpretation, we can suggest that the cause of AUB is from non- structure entities (COEIN).

The patient claimed to have had menstruation for 10−14 days with 4−5 times changing pads. The correlation between history taking (the patient's history of large bruises from minor injuries and history of

frequent bleeding from gum and laboratory finding (decrease platelet count and decrease hemoglobin) suggest AUB-C.

VWF is a plasma protein that intervenes with the initial adhesion of platelets at sites of vascular injury and also binds and stabilizes blood clotting factor VIII (FVIII) in the circulation. Impairing platelet adhesion or reducing the concentration of FVIII can cause bleeding in the defected von Willebrand factor. The symptoms of vWF factor defects can be frequent large bruises from minor bumps or injuries, extended bleeding from the gums after a dental procedure, and heavy or extended menstrual bleeding in women. The prevalence of von Willebrand disease was 10.9% range 7−20% among patients with menorrhagia compared to 1.3% in the general population [12].

Patients with VWD may present with severe mucosal bleeds (due to platelet dysfunction) and prolonged bleeding (due to factor VIII deficiency). The autosomal inheritance pattern means equal predilection of disease in both sexes. However, there is a higher incidence of symptomatic and apparent disease in women due to the hemostatic challenges faced during menstruation and childbirth [13].

A history of recurrent and prolonged bleeding, easy bruising, and any other forms of mucocutaneous bleeds should prompt us in the direction of VWD. In such cases, an ideal panel of tests should include APTT, PT, bleeding time, factor VIII: C Ristocetin cofactor, and VWF antigen assay.

Up to 13% of with heavy menstrual bleeding have some variant of von Willebrand disease and up to 20 % of women may have an underlying coagulation disorder. Therefore, the initial screening for possible bleeding disorders through the history can be asked about the following things [1]:

1. Heavy bleeding since the first menstruation
2. One of the criteria below:
   a. Have you ever had postpartum hemorrhage?
   b. Bleeding occurs during surgery
   c. Bleeding occurs during dental procedures
3. Two or more of the following criteria
   a. Ecchymosis 1−2 times per month
   b. Epistaxis 1−2 times per month
   c. Frequent bleeding gums
   d. Family history of bleeding disorders.

If one of the three criteria above is found, it is said to be positive screening and referral for further evaluation is needed. The patient reported history of frequent bleeding gum, large bruises from minor injury and history epistaxis; thus, the further evaluation can be done.

The treatment of choice in mild forms is the synthetic agent desmopressin. In patients with severe type 1, 2, and 3 diseases or in people who do not respond to desmopressin, the appropriate treatment is factor VIII concentrate which is rich in VWF [14].

Increased levels of VWF: Ag at the time of diagnosis of acute lymphoblastic leukemia (ALL) have been reported with a lot of variable response of VWF: Ag levels. It is postulated that peripheral lymphoblasts activate the endothelium and lead to elevation of VWF: Ag [14].

Acute lymphocytic leukemia (ALL) is a B or T lymphoblast malignancy characterized by the uncontrolled proliferation of abnormal, immature and pro, and genitor lymphocytes that ultimately lead to the replacement of elements of the bone marrow and other lymphoid organs, resulting in a disease pattern that is characteristic of the acute lythe lymphocytic disease [15].

The most common laboratory abnormalities in ALL include anemia, thrombocytopenia, neutropenia, and leucopenia or leukocytosis [15].

In this patient, significant thrombocytopenia was present. Decrease hemoglobin and leukocyte were also present, known as pantocytopenia.

AUB in ALL is often caused by thrombocytopenia. Thrombocytopenia with a decrease in several other cells is known as pancytopenia (decrease in hemoglobin, leukocyte, and platelet). Thrombocytopenia can cause AUB and it can be categorized into several types [15].

(1) Increased platelet destruction as in ITP, (2) decreased platelet production as in hematopoietic malignancies, and (3) increased sequestration as in splenomegaly.

Management of acute abnormal uterine bleeding (AUB) depends on the clinical condition, the possible etiology of the results of the assessment, the patient's desire to have children, and the patient's comorbid conditions. Treatment options for acute AUB are pharmacological or operative. Pharmacological treatment can be given through hormonal preparations (combined contraceptive pills) or non-hormonal (NSAIDs or anti-fibrinolytic agents). In addition, oral or parenteral iron preparations can be given to treat anemia in patients [10].

Conclusion

Abnormal uterine bleeding (AUB) is often found in women during their reproductive years throughout the world. The prevalence of AUB in women of reproductive age is around 3−30%. Approximately one-third of all women will experience uterine bleeding during their lifetime [1].

The causes of abnormal uterine bleeding may be abbreviated as "PALM-COEIN," including polyps,

adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; and iatrogenic; not yet classified. In general, the components of the PALM group are commonly for structural entities that can be measured visually by imaging and/or histopathology techniques, whereas the COEIN group is associated with entities that are not defined by imaging or histopathology (non-structural) [1], [3].

To diagnose an abnormal uterine bleeding disorder (AUB), first begins by evaluating the amount of blood loss during menstruation and the symptom which affect the patient. This is followed by a physical and supporting examination [14]. Up to 13% of with heavy menstrual bleeding have some variant of von Willebrand disease and up to 20 % of women may have an underlying coagulation disorder.

Management of acute abnormal uterine bleeding (AUB) depends on the clinical condition, the possible etiology of the results of the assessment, the patient's desire to have children, and the patient's comorbid conditions [10].

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