Case Report

Severe uterine hemorrhage as first manifestation of acute leukemia

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Abstract. Abnormal uterine bleeding is one of the most common presentations in gynecology practice with too many causes. Acute promyelocytic leukemia is one of the serious causes of uterine hemorrhage. Frequency and severity of hemorrage seen in acute promyelocytic leukemia is often associated with disseminated intravascular coagulation which can be life-threatening. A 37-year-old women was admitted to the emergency room with acute severe uterine bleeding, increasing weakness and weight loss. There was no gynecologic pathology that could clarify the situation. High suspicion of acute promyelocytic leukemia was noticed during evaluation. All-trans retinoic acid treatment with aggressive blood product support was started immediately. Pathological examination of sternal bone marrow confirmed the suspicions. Our aim is to report a case of massive uterine hemorrhage leading to diagnosis of acute promyelocytic leukemia for the first time and to take attention on acute promyelocytic leukemia as a very rare cause of uterine hemorrhage.

Key words: Uterine hemorrhage, thrombocytopenia, acute promyelocytic leukemia, anemia

1. Introduction

Abnormal uterine bleeding (AUB) is one of the most common presentations in gynecology practice. It is estimated that at least 5–10% of women of reproductive age will seek medical attention for menorrhagia (1). There are many causes of uterine hemorrhage. Pregnancy and pregnancy related complications must initially be excluded especially in the reproductive age patients. The evaluation of AUB should include an assessment of the pelvic organs and should be treated accordingly. If gynecological examination reveals no pathology, other reasons have to be taken into consideration before accepting situation as dysfunctional uterine bleeding. Adverse drug effects, nutritional deficiencies, renal insufficiency, hepatic abnormalities, vasculitis and especially hematologic disorders could be the reason for abnormal uterine bleeding. Acute promyelocytic leukemia (APL) is one of the serious reasons of uterine hemorrhage. The signs and symptoms of APL are usually nonspecific. But, uterine bleeding caused by disseminated intravascular coagulation (DİC) as a complication of APL can be life-threatening. So, early diagnosis and treatment of APL is very important.

According to our knowledge, there are a few documented cases of uterine hemorrhage leading to the diagnosis of APL (2,3). We report a very rare case of massive uterine hemorrhage together with hemodynamic instability as the first symptom for APL with severe anemia and thrombocytopenia.

2. Case report

A 37-year-old women was admitted to the emergency room with acute severe uterine bleeding. She reported vaginal bleeding during the preceding three days and experiencing

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increasing weakness and weight loss of four kilograms during the past two mounts. On admission the patient was pale, exhausted, hardly walking alone, the blood pressure was 70/40 mm Hg, pulse rate 110/min and filliform in nature. Gynecologic examination showed excessive uterine bleeding, normal cervix, uterus and ovaries. On vaginal ultrasonography, there were free fluids in Douglas' septum, both ovaries and uterus were normal, endometrial thickness was surprisingly very thin, thinner than 2mm. The complete blood count results revealed normal white blood cell count ($4,78x10^9$/L), severe anemia (hemoglobin: 7,8g/dl, haematocrit 22%, MCV: 91,3fl) and thrombocytopenia ($17x10^9$/L). For the diagnosis and treatment of acute severe uterine bleeding, urgent endometrial curratage was made.

Because of signs of hemodynamic instability, intensive fluid replacement by intravenous crystalloid, colloid solutions and two packs of red blood cells was initiated. During transfusion of second pack of red blood cells, mild transfusion reaction was noticed, immediately transfusion stopped and treatment of reaction applied accordingly. In the meantime, for investigation of the reason of hemorrhage and thrombocytopenia peripheral blood smear was performed. Peripheral blood smear examination showed 88% abnormal promyelocytes with characteristic immature, bilobed, 'applecore' nucleus and heavily granulated cytoplasm diagnostic of APL. After suspicion of leukemia in the blood smear, patient was transferred to a local third stage university hospital, hematology department. Immediately after transport all-trans retinoic acid (ATRA) treatment with aggressive blood product support (two units of red blood cells and four units of platelets suspension) was planned on the same day of transportation according to suspicions of APL. Sternal bone marrow examination revealed replacement by the leukemic cells (promyelocytes) a subtype of acute monocytic leukemia-M3 of the French-American-British (FAB) classification (4). Patient survived during the ATRA plus anthracycline based induction therapy period of treatment and achieved complete remission after four cycle consolidation chemotherapy. During hematological treatment period, subcutaneous injection of a GnRH agonist goseralin acetate was used for menstrual bleeding prophylaxis.

3. Discussion

AUB is a common gynecologic problem which can occur at any age. There are many causes of AUB, but the most common cause is a hormone imbalance called as dysfunctional uterine bleeding (2). Other possible causes of abnormal vaginal bleeding are the whole genital tract, the gastrointestinal tract and the urinary tract pathologies, adverse drug effects, nutritional deficiencies, systemic diseases such as vasculitis, thyroid disease and especially hematologic disorders and complications of pregnancy (1). Its management is complex. Therefore, for an accurate diagnosis; pelvic examination should be done together with abdominal examination. And also, a full blood count should be asked from all women with AUB. Ultrasound is the first-line diagnostic tool for identifying structural abnormalities. The diagnosis of our patient was made in this manner. First of all a hematological disorder was suspected because of serious thrombocytopenia revealed by complete blood count. And subsequently a high suspicion of APL was made according to peripheral blood smear findings, done to explain thrombocytopenia and hemorrhagia.

Hematological causes of uterine hemorrhage are often under-diagnosed during assesment in gynecology units. In fact, menorrhagia may be the first clinical manifestation of a bleeding disorder because any defect in the system can result in menorrhagia. The interaction of numerous coagulation and fibrinolysis factors and inhibitors, hormonal factors and platelets are required for haemostasis. Platelet adhesion, aggregation and fusion along with secretion of pro-coagulant factors create a platelet plug and contribute to haemostasis. Defects at any stage can result in increased bleeding. Therefore timely diagnosis and management is essential. The predominant hematological disorders causing acquired thrombocytopenia are immune thrombocytopenia purpura, aplastic anemia, acute leukemia and hipersplenism.

APL is a subtype of acute myeloid leukemia (AML) with distinctive biologic and clinical features. The disease is relatively rare in adults, accounting for only 10% to 15% of AML each year (5). Most patients are young, present with leukopenia, and exhibit a life-threatening coagulopathy. Our patient was 37 years old. APL is particularly associated with major coagulation disturbance historically resulting in fatal haemorrhage in up to 20% of patients during the presentation period (6). The haemorrhage of APL has been characterized as a form of disseminated intravascular coagulation (DIC) and thrombocytopenia. Thrombocytopenia is usually attributed secondary to bone marrow failure. The

mechanism of the coagulopathy is more complex than that of the conventional DIC associated conditions such as obstetric emergencies. DIC; seen in over 90% patients, because of severe fibrinolysis that has recently been shown to result from the expression of Annexin II, a receptor for fibrinolytic protein, on the surface of the leukemic cells (malignant promyeloctyes) (7). These promyelocytes release procoagulant substances (plasminogen activators, elastase) that activate the coagulation cascade, generate thrombin and deplete fibrinogen, clotting factors and platelets.

Heavy hemorrhages can be the first sign in at least 80% of cases of APL especially in the initial stage of the disease (8). In our case, the first sign is abnormal uterine bleeding. Fifty percent of the deaths occurred within the first week of treatment despite intensive blood product support (9). Thus, the treatment of patients with APL represents a true emergency primarily because of bleeding, which continues to represent a major cause of early death (10). Once the diagnosis is suspected on the basis of clinical findings and the peripheral blood smear (even without waiting for a bone marrow examination), treatment must be started immediately before confirmation of diagnosis by cytogenetic or molecular studies because very aggressive supportive care measures are critical during the first few days of therapy in APL than those with any other subtype of AML. Blood product supportive therapy strategies should be governed by the degree of bleeding and the pattern of coagulation test abnormalities.

The clinical signs of hemorrhage occur when the platelet count falls below $50X10^9$/L (11). It became common practice to transfuse platelets prophylactically for platelet counts of $20x10^9$/L. It has in fact been suggested that maintaining a platelet count $>50x10^9$/L during the first 10 days of treatment especially in those who are actively bleeding will minimize the risk of early haemorrhagic death (12). Platelet transfusion therapy has clearly decreased the hemorrhagic morbidity and mortality associated with hypoproliferative thrombocytopenia. Platelet and if necessary cryoprecipitate should be transfused multiple times a day during the first week or until the coagulopathy resolves (9).

All-trans retinoic acid (ATRA) has revolutionised the treatment of APL. The main strategy in the management of APL coagulopathy is early initiation of ATRA. This results in prompt resolution of the bleeding tendency and rapid normalisation of coagulation tests and fibrinogen (13). When combined with chemotherapy, long term survival rates of up to 80% can be achieved (14). APL represents the first example of a malignant disease that is highly curable with molecularly targeted therapy against its specific genetic abnormality. But the most important point is to start ATRA treatment at the earliest suspicion of APL. In our patient the ATRA treatment was started immediately after the diagnosis of APL was suspected.

4. Comments

The case emphasizes the importance of suspecting and investigating unusual causes of acute uterine bleeding when clinical picture suggests such a possibility. Particularly if the cause happens to be leukemia energetically treating may prove to be life saving. Especially if the diagnosis is APL, patients must be managed aggressively with blood product support and treatment of ATRA must be initiated at the earliest suspicion in order to minimize the risk of early haemorrhagic death. Modulation of the bleeding tendency should result in a reduction in early mortality and further improve the long term survival in this good prognosis sub-type of acute myeloid leukaemia.

References

1. Oehler MK, Rees MC. Menorrhagia: an update, Acta Obstet Gynecol Scand 2003; 82: 405-422.
2. Falcone T, Desjardins C, Bourque J, et al. Dysfunctional uterine bleeding in adolescents. J Reprod Med 1994; 39: 761-764.
3. Alperin M, Quaas A, Johnson NR, Hornstein MD. Endometrial ablation in a woman with a persistent uterine hemorrhage due to acute promyelocytic leukemia: a case report. J Reprod Med 2007; 52: 548-550.
4. Bennett JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group. Ann Intern Med 1985 103: 620-625.
5. Tallman MS, Nabhan C, Feusner JH, Rowe JM. Acute promyelocytic leukemia: evolving therapeutic strategies. Blood 2002; 99: 759-767.
6. Warrell RP, de The H, Wang Z-Y, Degos L. Acute promyelocytic leukaemia. N Engl J Med 1993; 329: 177-189.
7. Hajjar KA, Acharya SS. Annexin II and regulation of cell surface fibrinolysis. Ann N Y Acad Sci 2000; 902: 265-271.
8. Fenaux P, Chomienne C, Degos L. Treatment of acute promyelocytic leukaemia. Best Practice & Research Clin Haematol 2001; 14: 153-174.
9. Tallman MS, Brenner B, Serna Jde L, et al. Meeting report: acute promyelocytic leukemiaassociated coagulopathy, 21 January 2004, London, United Kingdom. Leuk Res 2005; 29: 347-351.

10. De la Serna J, Montesinos P, Vellenga E. Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. Blood 2008; 111: 3395-3402.
11. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. Br J Haematol 2003; 122: 10-23.
12. Falanga A, Rickles FR. Pathogenesis and management of the bleeding diathesis in acute promyelocytic leukaemia. Best Practice & Research Clin Haematol 2003; 16: 463-482.
13. Kawai Y, Watanabe K, Kizaki M, et al. Rapid improvement of coagulopathy by all-trans retinoic acid in acute promyelocytic leukemia. Am J Hematol 1994; 46: 184-188.
14. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans retinoic acid in acute promyelocytic leukemia: longterm outcome and prognostic factor analysis from theNorth American Intergroup protocol. Blood 2002; 100: 4298-4302.