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An atypical presentation of endometrial cancer as angina secondary to critically low hemoglobin and iron deficiency associated pancytopenia: A case report

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ABSTRACT

Endometrial cancer is the most common type of gynaecological cancer in high-income countries. Abnormal uterine bleeding (AUB) is the most common symptom of endometrial cancer; however, patients can often present in an atypical fashion. This case is an example of an atypical presentation of endometrial cancer, with angina secondary to severe iron deficiency anemia, and a rare example of pancytopenia secondary to iron deficiency.

A 46-year-old nulliparous woman with no past medical history presented to the emergency department with acute chest pain. All her vitals were normal. The ECG showed T-wave inversion with a negative serum troponin. She had obvious pallor but appeared well. She had a critical hemoglobin of 1.9 g/dL and severe iron deficiency with a plasma iron level of <2 μg/L. In the 6 months leading up to her presentation, she had heavy and prolonged menstruation of up to 10 days.

She received a total of 6 units of packed red blood cells and an iron infusion. Her chest pain resolved, and her pancytopenia corrected following replenishment of iron stores. She underwent a laparoscopic total hysterectomy, bilateral salpingo-oophorectomy for stage 1b, grade 2 endometroid adenocarcinoma.

This is one of the lowest hemoglobin levels recorded in a hemodynamically stable patient with endometrial cancer, and the only case report of iron deficiency induced pancytopenia secondary to abnormal uterine bleeding. This case is a reminder that female patients with angina should have their hemoglobin checked, and patients with anemia should have a thorough review of their gynaecological history.

1. Introduction

Endometrial cancer is the most common type of gynaecological cancer in high-income countries and the fourth most common type of cancer in women overall [1]. Between 75% and 90% of patients with endometrial cancer will present with abnormal uterine bleeding (AUB) [2,3]. The definition of abnormal bleeding encompasses irregular or anovulatory cycles, prolonged or heavy bleeding and intermenstrual bleeding. When AUB is heavy or chronic, severe life-threatening anemia can occur, and the underlying cause should be investigated to rule out malignancy [4]. Unfortunately, recent international surveys indicate there are still many barriers to women seeking investigation and treatment for AUB, and many women do not seek care [5]. While it is relatively common for women with AUB to suffer with iron deficiency anemia [4], pancytopenia secondary to iron deficiency is extremely rare, with only a handful of case reports in the literature [6–8].

This case details a highly atypical presentation of endometrial cancer, in a woman whose presenting complaint was angina. She was found to be profoundly anemic and pancytopenic with a hemoglobin of just 1.9 g/dL, one of the lowest levels to be reported in a hemodynamically stable patient.

2. Case Presentation

A 46-year-old nulliparous woman presented to the emergency department with acute retrosternal chest pain and mild shortness of breath. She had no previous medical history and took no regular medications. Other than a BMI of 29, no other cardiovascular risk factors were elicited from the patient's history. On review she was normotensive, a heart rate of 60 beats/min, normal oxygen saturations and a

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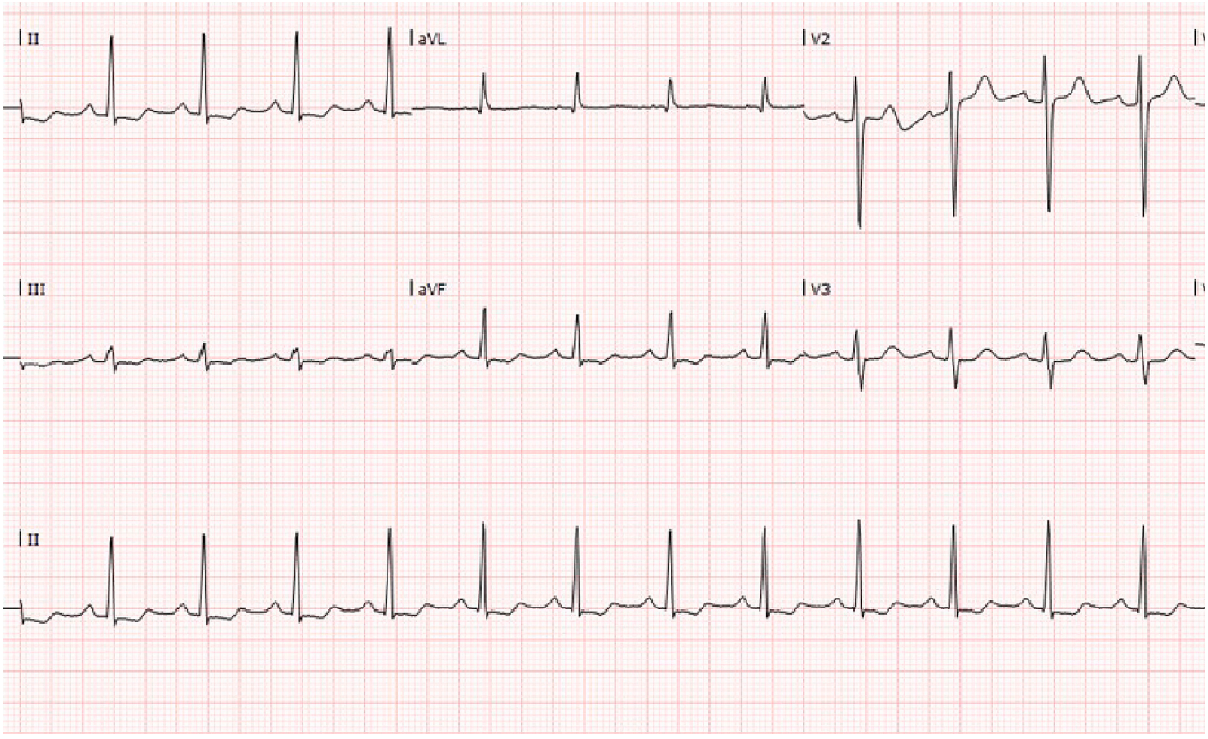

Fig. 1. ECG at initial presentation showing T-wave inversion.

Table 1
Laboratory results on admission and following treatment, 3 weeks following first presentation.

Test	Result at presentation	Results 3 weeks later	Reference range
Hemoglobin	19	139	115-160 g/L
White cell count	2.17	4.18	4.00–11.00
Platelet count – blood	138	166	150–400
Red cell count	1.58	4.75	3.80–4.80
Haematocrit	0.09	0.42	0.37–0.47 L/L
Mean cell volume - blood	54	89	80–100 fL
Red cell distribution width	21.7	14.9	9–15 CV%
Neutrophils absolute	1.45	2.66	2.00–7.50
Lymphocytes absolute	0.53	1.76	1.20–4.00
Monocytes absolute	0.19	0.31	0.20–1.00
Ferritin – serum	<1	28	30-300 µg/L
Iron – plasma	<2	14	9–30 µmol/L
Transferrin – plasma	39	26	23–46 µmol/L
Transferrin saturation – plasma	<3	27	13–45%
Vitamin B12 - Serum	170	–	140–770
Folate – serum	28.6	–	>7.0 nmol/L
Prothrombin M2	15.7	–	12.0–16.5 s
INR	1.1	–	0.9–1.3
APTT	30.1	–	27.5–38.5 s
Fibrinogen – plasma	3.3	–	2.0–4.0 g/L

respiratory rate of 14. The ECG showed widespread T-wave inversion (Fig. 1) with a negative serial serum troponin.

Her initial laboratory results showed an astonishingly low hemoglobin of 1.9 g/dL. The laboratory results are summarized in Table 1. Iron studies showed a severe iron deficiency anemia with a plasma iron level of <2 µg/L. Folate and B12 levels were normal. The morphology of erythrocytes was consistent with severe microcytic anemia. The peripheral smear showed significant microcytosis, anisocytosis and hypochromia with pencil cells and occasional teardrop cells. There was neutropenia with some hypersegmented neutrophils and mild thrombocytopenia with normal platelet morphology.

The diagnosis of critical anemia prompted a more extensive history. She reported erratic menstrual cycles since menarche at the age of 13 and anovulatory cycles with up to 6 months of amenorrhoea at a time. In the 6 months leading up to her presentation, she had very heavy menstrual cycles and prolonged menstruation of up to 10 days. She had never presented to a doctor in relation to her symptoms and thus her bleeding had never been investigated. She had never had a cervical screening test. Despite her critical anemia, she was otherwise well and had a normal exercise tolerance.

Physical examination revealed signs of anemia, including whole-body pallor and a loud ejection systolic murmur on cardiac auscultation. Gynaecological examination was normal other than an enlarged 14-week-size uterus.

A pelvic ultrasound scan showed a bulky uterus with heterogenous morphology compatible with adenomyosis. There was markedly thickened, irregular and hypervascularized endometrium, with thickness of 33 mm. The left ovary was enlarged, measuring 78 cc, and containing a 51x46x39mm simple cyst. The right ovary was normal. Endometrial pipelle sampling showed endometrioid adenocarcinoma, grade 1–2. Computerized tomography of the chest, abdomen and pelvis showed no evidence of metastases.

She was treated with 6 units of packed red blood cells and an iron infusion. Following transfusion, the T-wave inversion on ECG resolved, along with her chest pain (Fig. 2). For management of her bleeding, medroxyprogesterone was commenced at a dose of 10 mg three times a day, with oral tranexamic acid 1000 mg three times a day. She was discharged after two days and referred to the specialist gynaecology oncology team. She later underwent a laparoscopic total hysterectomy, bilateral salpingo-oophorectomy and sentinel lymph node biopsy. This histopathology revealed a stage 1b, grade 2 endometroid adenocarcinoma. She received vault brachytherapy and was doing well at her last follow-up.

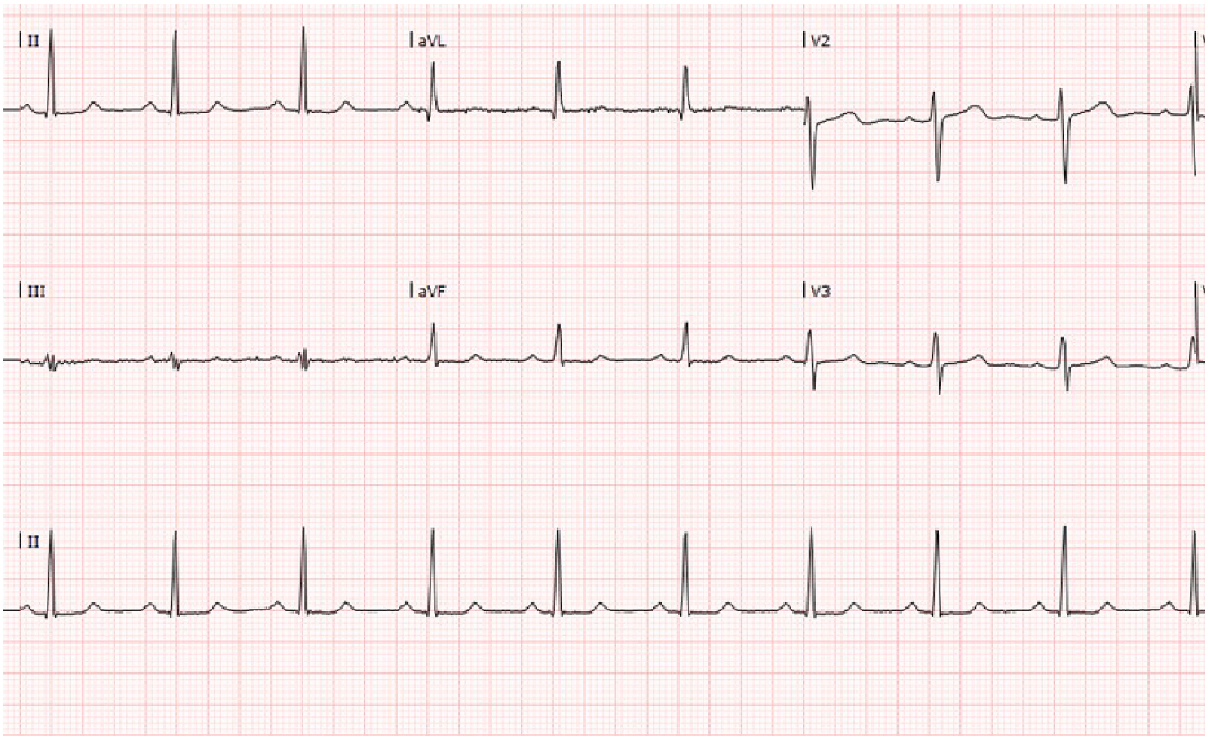

Fig. 2. ECG after transfusion, showing resolution of T-wave inversion.

3. Discussion

This case highlights the severity of anemia that can result from AUB. It demonstrates that endometrial cancer and severe anemia can present in a very atypical fashion and a gynaecological history is always an important part of taking a medical history. It is an important reminder that AUB is a symptom and not a diagnosis and should be investigated to treat the underlying cause.

This is perhaps the lowest hemoglobin reported in a woman with endometrial cancer, and one of the lowest reported levels in a non-trauma patient who remains hemodynamically stable. There are other cases reporting critically low hemoglobin associated with AUB, but none of these patients had pancytopenia. A case of a 42-year-old woman with menorrhagia was reported with a hemoglobin of 1.4 g/dL but she was symptomatic with anemia, experiencing dizziness, fatigue and shortness of breath, and had normal platelet and white cell counts [9]. A case of a 21-year-old with AUB and a hemoglobin of 1.7g/dL was reported, but this patient was hemodynamically unstable with hypotension and tachycardia, and no associated pancytopenia [10].

This patient had a very atypical presentation of endometrial cancer, with her primary presenting complaint being angina. Cardiology was consulted and advised that given the history of a single episode of chest pain, along with negative serial troponins and resolution of ECG changes after transfusion, no further investigation was required in the acute setting. She was referred to a specialist gynaecology oncology hospital for further workup, including a pre-operative echocardiogram. While this patient had a clear reversible cause for her angina, clinicians should always consult their local institution's risk stratification protocol and refer for further investigations as needed based on the risk profile including: chest x-ray, echocardiogram, exercise stress testing, myocardial perfusion MRI or CT coronary angiogram [11].

In addition to critical anemia, she also had pancytopenia. The blood film changes seen were consistent with iron deficiency and there were no other features to suggest marrow infiltration by cancer. Her B12 and folate were normal, and her blood counts resolved after the correction of her iron deficiency. Without a bone marrow biopsy it is impossible to say if this was solely caused by iron deficiency; however, these features strongly support the diagnosis of iron deficiency induced pancytopenia (a very rare condition).

When correcting severe iron deficiency anemia, the overall clinical picture should be considered. Chronic, slowly progressive iron deficiency can be treated with iron infusion alone, without the need for blood transfusion, as the body has time to compensate for the anemia. Depending upon the degree of anemia, a second or third dose of intravenous iron may be required. Blood transfusion may be considered for those with critical anemia or myocardial ischemia, or for the hemodynamically unstable patient [12,13]. It can take some time for the anemia to correct following iron infusions; typically, the hemoglobin level should increase by 2g/dL within 4 to 8 weeks [13]. In this case, due to the patient's chest pain and ECG changes, as well as impending major surgery for her malignancy, there was some degree of urgency for correction of the anemia. Hence, she was treated with a combination of blood transfusion and intravenous iron infusion.

Endometrial cancer is an important differential in patients with AUB and endometrial sampling should be considered. All post-menopausal patients with bleeding should be offered imaging and/or sampling. From the age of 45 to menopause, endometrial sampling should be undertaken in those with heavy, prolonged or frequent bleeding. In someone under 45 years old with AUB, endometrial sampling should be considered if there are other risk factors for endometrial cancer, any patient over a BMI of 30, or persistent AUB [14].

Pelvic imaging with ultrasound can diagnose anatomical pathology such as fibroids, polyps or adenomyosis as a cause of AUB; however, in the pre-menopausal patient, a measurement of endometrial thickness is not a reliable alternative to endometrial sampling [15]. Endometrial sampling can be performed with a pipelle biopsy, or via hysteroscopy with endometrial biopsy. Pipelle sampling can be done quickly in the outpatient setting though it is a blind procedure and therefore focal pathology can be missed. Hysteroscopy has the advantage of direct vision, improving diagnosis of focal pathology such as polyps and fibroids which can be missed by Pipelle sampling alone. Additionally, hysteroscopy has both diagnostic and therapeutic modalities. However,

it can be more costly, often requiring analgesia/sedation and an operative setting [15]. Ultimately, the choice of sampling should depend on the preference of the patient and the clinical situation.

4. Conclusion

Endometrial cancer can have a very atypical presentation, with angina secondary to severe anemia. The workup of a patient with angina and anemia should include a gynaecological history and examination with consideration of endometrial sampling if the history indicates AUB. Iron deficiency is a rare cause of pancytopenia and bone marrow biopsy is warranted if it does not resolve following replacement of iron stores. Treatment of severe iron deficiency anemia is with intravenous iron; however, the clinical presentation and urgency to correct the anemia may warrant blood transfusion.

Contributors

Grace Crawford was involved in the conception of the case, literature review and drafting of the manuscript.

Amin Bahabri was involved in patient care, the conception of the case report, and manuscript editing and revision.

Stephanie P'ng contributed to the manuscript with critical edits and revision of the article for important intellectual content.

All authors approved the final submitted manuscript.

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Patient consent

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Provenance and peer review

This article was not commissioned and was peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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