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A Case of Recurrent Menorrhagia Caused by Severe Hypothyroidism in a Rural Kenyan Hospital: Clues from Madarosis, Milphosis, and Woltman's Sign

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Abstract: **The typical causes of premenstrual abnormal uterine bleeding (e.g., menorrhagia) are gynecologic and include pregnancy-related bleeding (e.g., abortion and ectopic pregnancy), fibroids, adenomyosis, endometrial hyperplasia, cervical and uterine cancers, etc., and medical causes like coagulation disorders. Hypothyroidism must be considered a cause of menorrhagia, especially in women on thyroid hormone replacement therapy (who are non-compliant) due to its suppressive effects on ovulation with subsequent estrogen-induced breakthrough bleeding, coupled with hypocoagulation and fibrinolysis. This case study from rural Kenya highlights how non-adherence to lifelong thyroxine replacement therapy led to profound hypothyroidism with classical physical findings and caused severe recurrent menorrhagia, which subsequently resolved with compliant treatment.**

Keywords: **menorrhagia, abnormal uterine bleeding, hypothyroidism, thyroxine, madarosis, milphosis, delayed tendon reflex, myxedema, Kenya.**

1. INTRODUCTION

Hypothyroidism is a clinical syndrome caused by a deficiency of thyroid hormones and is biochemically characterized by low serum concentrations of free thyroxine (fT4) and free triiodothyronine (fT3) and a correspondingly elevated serum level of thyroid stimulating hormone (TSH) due to a negative bio-feedback process (1). The disease can be overt (i.e., a low fT4 and fT3 and a high TSH) or subclinical (i.e., a normal fT4 and fT3 and a high TSH). The main causes of hypothyroidism include autoimmune thyroiditis (Hashimoto's disease) and iatrogenic causes like total thyroidectomy, radioiodine therapy, and external neck radiation for various cancers. Other causes include drugs (e.g., lithium, amiodarone, etc.), infiltrative

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diseases (e.g., hemochromatosis, scleroderma, etc.), and any causes of hypopituitarism (e.g., Sheehan's syndrome, head trauma, etc.). (2). The two main mechanisms underpinning the clinical manifestations of hypothyroidism reflect a general slowing of the metabolic processes and the deposition of glycosaminoglycans in the interstitial tissues of many organs (3). The former mechanism leads to fatigue, slow movement, slow speech, bradycardia, cold intolerance, constipation, weight gain, and delayed relaxation of deep tendon reflexes (which is called Woltman's sign if occurring in the ankles). The latter mechanism may lead to a non-pitting edema (myxedema), coarse hair and skin, puffy facies, enlargement of the tongue, and hoarseness of the voice (2). Myxedema may involve multiple organs and cause altered mental status, including coma (4). Patients with hypothyroidism related to thyroid cancer may have their hair become dry, thin, brittle, and prone to breakages and losses on the scalp (alopecia), the eyebrows (madarosis), and eyelashes (milphosis) (5). Hypothyroidism may cause anemia due to bone marrow suppression, decreased erythropoietin production, comorbid diseases, or concomitant iron, vitamin B12, or folate deficiency. Normocytic normochromic anemia is the most common form encountered in hypothyroidism (6). In women of reproductive age, hypothyroidism may cause two clinical entities: oligomenorrhea-amenorrhea or hypermenorrhea-menorrhagia. Severe hypothyroidism is commonly associated with moderate to severe menorrhagia. The mechanism of menorrhagia in hypothyroidism is linked to estrogen breakthrough bleeding following anovulation induced by increased prolactin levels. Prolactin is increased in hypothyroidism because thyrotropin-releasing hormone (TRH) increases the secretion of both TSH and prolactin (7). Additionally, hypothyroidism is associated with decreased levels of clotting factors VII, VIII, IX, and XI and an increased shift towards fibrinolysis (8). Besides, hypothyroidism has been linked to an acquired form of von Willebrand's syndrome type 1 (9). All these lead to a hemostatic defect, which also contributes to menorrhagia. When thyroid hormone replacement is achieved with oral levothyroxine, the TSH levels normalize within 3 to 6 months, and the abnormal uterine bleeding resolves within a few days to a few weeks (10, 11, 12).

2. CASE SUMMARY

Presenting illness and physical examination

A 43-year-old single mother of 7, a businesswoman from Njoro, Nakuru County, Kenya, first presented to us in November 2020 with severe symptomatic microcytic hypochromic anemia (hemoglobin [Hb] was 6 g/dL with a mean corpuscular volume [MCV] of 55 femtoliters [fL]) for blood transfusion. She had experienced menorrhagia for 5 months prior and had been undergoing management in her local health center with combined oral contraceptives and hematinics for an apparent "hormonal imbalance." Importantly, she had undergone a thyroidectomy in 2015 for a goiter whose histology had confirmed a papillary carcinoma of the thyroid gland. She had subsequently undergone a radioactive iodine ablation and had been put on lifelong oral levothyroxine replacement, for which she claimed compliance at a dose of 50 mcg daily. However, she had long stopped attending her oncology clinic appointments in Nairobi (a distance of about 160 km by road) due to financial challenges. She had irregular menstrual periods with up to 3-6 months of amenorrhea at a time since the surgery, and she was sexually inactive. Her last delivery was in 2014. She had no features of gastritis, constipation, or melena stool, had normal bowel movements, and had no cough or constitutional symptoms. Her clinical examination was significant for severe conjunctival and buccal mucosal pallor, a thyroidectomy scar, and vague suprapubic tenderness with no abdominal organomegaly. Speculum and digital vaginal examinations showed fresh and clotted blood in the vaginal introitus but no other significant lesions. She had normal S1 and S2 heart sounds, but with a hemic murmur and an S3 gallop, and was not in obvious fluid overload. She had mild bipedal, non-pitting edema. The rest of the exam was unremarkable.

Diagnostic workup and management

Her pregnancy test was negative. An abdominopelvic ultrasound showed no fibroids, a normal endometrial thickness, and no cervical lesions. An interval cervical Pap smear was negative for any metaplasia or neoplastic changes. The complete blood count showed a total leucocyte count of 6.4 $x10^3$/µL, a Hb of 6 g/dL, an MCV of 55 fL, and a total platelet count of 534 $x10^3$/µL. The random blood sugar, renal, and liver panels were normal. The thyroid profile showed a total T3 of 1.36 nmol/L [1.2-3.1], a total T4 of 121.94 nmol/L [68-140], and a TSH of 94 mIµ/L [0.5-5]. She was HIV negative. In this presentation, she was managed with blood transfusion, intravenous, then oral tranexamic acid, oral ferrous sulfate with vitamin C to promote iron absorption, and supportive care. She claimed adherence to levothyroxine treatment. The vaginal bleeding ceased after 1 day of intravenous tranexamic acid. She was discharged home stable after 2 days with a Hb of 10.2 g/dL on hematinics and levothyroxine 100 mcg daily and advised on adherence to medications. She did not attend a scheduled clinic appointment two weeks later and was lost to follow-up thereafter.

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Readmission in severe hypothyroidism: - Management and follow-up

In June 2023, she re-presented with active menorrhagia (changing 8-12 fully soaked pads every 12-24 hours) complicated with severe symptomatic iron deficiency anemia (Hb of 11 g/dL with MCV of 75 fL, but she was paper-white pale and severely dehydrated, hence the Hb was deemed to be hemoconcentrated) and features of high-output heart failure. She reported having had blood transfusions on three other separate occasions in other hospitals due to the same problem between 2021 and 2022. At that time, she had a repeat Pap smear, which was negative, two pelvic ultrasounds, which were normal, and had been scheduled in another hospital for a diagnostic endometrial fractional curettage and biopsy. She had actually come back to us for a possible hysterectomy to ensure a "final solution" to the menorrhagia. She had a BP of 100/60 mmHg, a pulse rate of 71 bpm, and was afebrile. Notably, she had quite obvious loss of eyebrow hairs bilaterally in the lateral regions (i.e., 'madarosis'), bilateral loss of eyelashes in the lateral aspects ('milphosis'), loss of hair on the scalp more prominent in the fronto-parietal regions (alopecia), and moderate bilateral periorbital edema, more prominent on the left eye. See figures 1 to 3 below.

Figure 1: There is loss of eyebrow hairs bilaterally in the lateral regions, called 'madarosis.'

(Photos taken and posted with the full written informed consent of the patient.)

Figure 2: There is bilateral loss of eyelashes in the lateral aspects, called 'milphosis' and marked with the blue arrows. There is also moderate bilateral periorbital edema, more prominent on the left eye and marked with the red arrow.

(Photos taken and posted with the full written informed consent of the patient.)

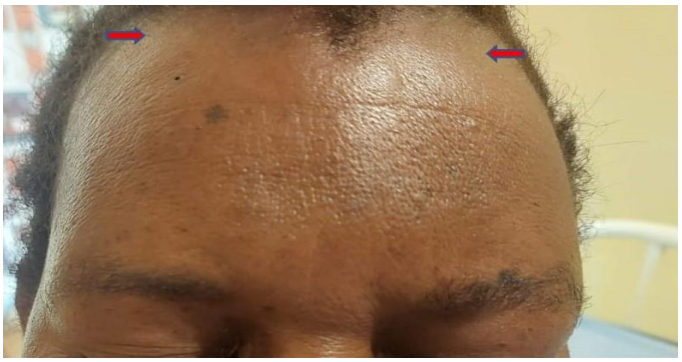

Figure 3: There is loss of hair on the scalp more prominent in the fronto-parietal regions (i.e., alopecia) marked with the red arrows.

(Photos taken and posted with the full written informed consent of the patient.)

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She had bilateral non-pitting grade 2 edema (myxedema), elevated JVP to about 6 cm, normal S1 and S2 with an S3 gallop, and a hemic murmur. Her abdominal exam was unremarkable. Speculum and digital vaginal examinations showed active uterine bleeding with fresh blood in the vaginal introitus but no other lesions. A neurological exam revealed markedly delayed relaxation of the ankle jerks (Woltman's sign). The thyroid profile done in this admission showed profound hypothyroidism with a total T3 of 1.2 nmol/L [1.2-3.1], a total T4 of 48 nmol/L [68-140], and a TSH of >100 mIμ/L [0.5-5]. She admitted to being non-compliant with the levothyroxine due to financial constraints and had not been taking it for more than 3 to 6 months at any given time. Accordingly, we counseled her on the profound nature of her hypothyroidism, its direct role in the etiology of the menorrhagia, and the other clinical features she had. She was successfully managed with blood transfusion (under furosemide cover), tranexamic acid (the bleeding stopped completely within 8 hours of treatment), hematinics, and levothyroxine, whose dosage was now re-initiated at 200 mcg daily at discharge. We opted against hysterectomy and focused on treating the hypothyroidism. The siblings were involved in the counseling and committed to ensuring uninterrupted levothyroxine supply and compliance. One month after discharge, her thyroid profiles were markedly improved, and two months later, they were normal. (See table 1 below.) It is now 1 year later, and she remains stable on levothyroxine with normal menstrual periods, normal Hb, and resolution of the hair losses, albeit with residual mild pedal myxedema. She's since been reviewed by the oncologists, and she has no thyroid cancer recurrence. She's currently on follow-up at another health facility.

Table 1: Summary of Hemoglobin, MCV, Thyroid Profile, and Interventions.

DATE	Hb [11-16 g/dL]	MCV [80-99 fL]	Total T3 [1.2-3.1 nmol/L]	Total T4 [68-180 nmol/L]	TSH [0.5-5 mIμ/L]	Interventions
20/11/2020	6.0	55	1.36	121.94	94.89	Transfused 3 units, whole blood, Tranexamic acid, FeSO4, Vitamin C, Oral Levothyroxine 100 mcg/day
06/6/2023	11.0	75	1.2	48	>100	Transfused 1unit, whole blood, Tranexamic acid, FeSO4, Vitamin C, Oral Levothyroxine 200 mcg/day
06/07/2023	13.2	83	3.61	145.77	8.57	FeSO4, Vitamin C, Oral Levothyroxine 200 mcg/day
12/09/2023	12.6	82	2.94	166.31	4.38	Oral Levothyroxine 100 mcg/day

KEY: - FeSO4= ferrous sulfate tablets or syrup.

3. DISCUSSION

The causes of abnormal uterine bleeding [AUB] (i.e., bleeding that is of abnormal quantity, duration, or schedule) in a pre-menopausal woman include structural reproductive tract diseases (e.g., fibroids, endometrial polyps, adenomyosis, neoplasms, infections, trauma, pregnancy-related bleeding, etc.) or nonuterine causes (e.g., ovulatory dysfunction, hormonal imbalances, etc.). Iatrogenic causes include sex steroids, phenytoin, anticoagulants, and intrauterine contraceptive devices. Systemic causes include hypothyroidism, cirrhosis, and coagulation disorders (13). The approach to AUB in a pre-menopausal woman therefore needs a targeted history and physical examination, including a speculum and digital vaginal examination, which should pick out the most likely etiology. In clinical practice, the most likely etiologies are pregnancy-related bleeding (abortion and ectopic pregnancy), uterine fibroids, endometrial hyperplasia due to hormonal abnormalities, infections like cervicitis, and neoplasms like cervical cancers (14). In our patient, these causes were ruled out in each visit, leading to the diagnosis of profound hypothyroidism as the etiology for her severe menorrhagia. Gastrointestinal causes of iron deficiency anemia, e.g., peptic ulcer disease, and colorectal causes, were ruled out clinically. The fact that she had a history of amenorrhea for several months followed by severe menorrhagia underscores the pathogenetic mechanism in which hypothyroidism leads to anovulation (hence the amenorrhoeic periods), which is then followed by estrogen-induced breakthrough bleeding (hence the menorrhagia). Her rapid response to intravenously administered tranexamic acid (an anti-fibrinolytic agent), blood transfusion, and thyroid hormone replacement also underscores the second pathogenetic

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mechanism in which hypothyroidism causes a deficiency of some clotting factors and promotes fibrinolysis. In her first presentation to us in 2020, she was in subclinical hypothyroidism, as evidenced by normal levels of total T3 (TT3) and total T4 (TT4) and a markedly elevated TSH level. In our hospital, we use TT3 and TT4, as they're cheaper than the fT3 and fT4 assays yet give the same clinical information (15). When we readmitted her in 2023, she was in profound hypothyroidism, as evidenced by low levels of TT3 and TT4, and a very high TSH level. The hypothyroidism was caused by the thyroidectomy for papillary thyroid cancer and subsequent radioactive iodine ablation therapy, which made her dependent on thyroid hormone replacement for life. Unfortunately, due to financial challenges, she had been defaulting on levothyroxine medication for several months at a time, leading to profound hypothyroidism manifesting with severe menorrhagia and the other clinical findings described. The management of hypothyroidism includes treatment of the underlying etiology and thyroid hormone replacement therapy. For our patient, since involving her siblings in her care in 2023, she has been adherent to levothyroxine therapy. Subsequently, she has remained euthyroid, her monthly menstrual cycles have normalized, and she has had no further recurrence of menorrhagia. In retrospect, therefore, the recurrent menorrhagia was caused by severe hypothyroidism since it resolved with thyroid hormone replacement to a euthyroid status.

4. CONCLUSION

Hypothyroidism must be considered as a possible cause of menorrhagia (or premenopausal AUB), where the other more "traditional" gynecological causes have been ruled out. This is especially true for patients who have had a thyroidectomy for any reason and/or are on thyroid hormone supplementation. In such cases, poor compliance with thyroxine treatment must be sought and addressed.

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Conflict of interests

The authors declare no conflicts of interest.

Ethical consideration

Written informed consent was obtained from the patient to publish this manuscript including the photo images attached.

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