JCEM Case Reports, 2023, **1**, 1–3
https://doi.org/10.1210/jcemcr/luad057
Advance access publication 8 June 2023
Case Report

Thalidomide-Induced Primary Amenorrhea in a Patient With HbE/Beta-Thalassemia

Arijit Singha,[1] Pradip Mukhopadhyay,[1] and Sujoy Ghosh[1]

[1]Department of Endocrinology & Metabolism, Institute of Postgraduate Medical Education & Research, Kolkata, West Bengal 700020, India

Correspondence: Sujoy Ghosh, DM, FRCP, FACE, Department of Endocrinology & Metabolism, Institute of Postgraduate Medical Education & Research, Kolkata, West Bengal 700020, India. Email: drsujoyghosh2000@gmail.com.

Abstract

An 18-year-old girl was evaluated for primary amenorrhea. She was diagnosed with hemoglobin E (HbE)/beta-thalassemia during childhood and needed blood transfusions every month to maintain adequate hemoglobin levels. She was started on thalidomide to reduce her transfusion requirements at 12 years of age and became transfusion independent after 6 months. She had normal stature and Tanner stage 4 sexual maturation, but she failed to attain menarche. Investigations revealed that she had elevated serum gonadotropin levels, indicating primary ovarian dysfunction. Her karyotype was 46,XX. Ultrasonographic examination demonstrated the absence of follicles in both ovaries. There was no evidence of abnormalities of the urogenital tract. Thalidomide was stopped, and she attained menarche spontaneously 3 months thereafter. Subsequently, her menstrual cycles were regular. Repeat ultrasound scans demonstrated the presence of ovarian follicles as well as an increase in ovarian volume. Mechanistic links between ovarian dysfunction and thalidomide remain to be found. One possibility is impaired blood flow and follicular development.

Key Words: primary amenorrhea, thalidomide, ovarian dysfunction, HbE/beta-thalassemia

Abbreviation: HbE, hemoglobin E.

Introduction

Thalidomide was developed in Germany in 1956 and was used initially as a sedative. Later it was used in pregnant women for the treatment of morning sickness but the drug's devastating teratogenic side effects led to its withdrawal in 1961. The immunomodulatory and/or anti-inflammatory property of thalidomide has been established, and the drug has been used for various clinical conditions, including multiple myeloma and erythema nodosum leprosum. Off-label uses of thalidomide include for aphthous ulcers, cutaneous lupus, or inflammatory bowel disorder [1, 2]. Recent evidence suggests a possible role of thalidomide in myeloproliferative disorders, sickle cell disease, and thalassemia. By promoting the expression of the γ-globin gene, thalidomide increases fetal hemoglobin levels and can significantly reduce a patient's transfusion burden. Moreover, it increases the lifespan of erythrocytes without having any demonstrable effects on white blood cells or platelets [3].

The use of thalidomide is associated with various side effects, including constipation, drowsiness, and peripheral neuropathy. Few cases of secondary amenorrhea following thalidomide therapy have been reported [4]. Herein, we describe a case of primary amenorrhea due to ovarian dysfunction in a patient with hemoglobin E (HbE)/beta-thalassemia on thalidomide therapy, which normalized following cessation of thalidomide therapy.

Case Presentation

An 18-year-old girl presented to our clinic for evaluation of primary amenorrhea. She was diagnosed with HbE/beta-thalassemia at the age of 5 years. Initially, she required blood transfusion every month, but with the initiation of thalidomide (100 mg/day) at 12 years of age, she was no longer transfusion dependent after 6 months. Iron chelation therapy was started at 7 years of age, and she was on deferasirox tablets 1000 mg per day at the time of evaluation. She noticed thelarche at 10 years of age, and pubarche occurred later. She had no history of use of exogenous gonadal steroids. She did not complain of periodic lower abdominal pain. She had no history suggestive of autoimmune disorders, hirsutism, or galactorrhea. She did not have any symptoms of headache, visual disturbances, vomiting, or hot flashes. There was no family history of premature ovarian insufficiency or delayed menarche.

Diagnostic Assessment

Her height was 154 cm (~ 50th percentile), height SDS 0.85, upper segment: lower segment ratio 0.88, body mass index 23 kg/m^2. Physical examination showed that her sexual maturation rating was Tanner stage 4. Mild pallor and hepatosplenomegaly were present. Features of other causes of primary amenorrhea, including Turner syndrome, were absent. There were no clinical signs of hyperandrogenism. Goiter was absent. Bone age (by Greulich-Pyle radiographic assessment method) was not delayed. Serum gonadotropin levels were elevated: luteinizing hormone (LH) 44.9 mIU/mL (reference range, 1.10–11.6 mIU/mL) and follicle-stimulating hormone (FSH) 44.8 mIU/mL (reference range, 3.00–14.4 mIU/mL). Her estradiol was 220 pmol/L (60.0 pg/mL) (reference range,

Received: 23 April 2023. **Editorial Decision:** 1 May 2023. **Corrected and Typeset:** 8 June 2023

77.1–921.5 pmol/L [21.0–250.9 pg/mL]) and serum anti-Müllerian hormone (AMH) was 0.22 pmol/L (0.032 ng/mL) (reference range, 11.8–66.7 pmol/L [1.65–9.33 ng/mL]), which were low, suggesting the possibility of primary ovarian dysfunction (Table 1). Other hormonal evaluations revealed a serum prolactin of 5.3 mcg/L (5.3 ng/mL) (reference range, 1.90–25.0 ng/mL [1.90–25.0 mcg/L]); free thyroxine (T4) 1.17 ng/dL (reference range, 0.80-1.90); thyrotropin (TSH) 2.5 μIU/mL (reference range, 0.40–4.00); cortisol 344.8 nmol/L (12.5 mcg/dL) (reference range, 137.9–689.6 nmol/L [5.0–25.0 mcg/dL]); adrenocorticotropic hormone (ACTH) 9.46 pmol/L (43 pg/mL) (reference range, 2.2–10.12 pmol/L [10–46 pg/mL]); insulin-like growth factor 1 (IGF-1) 23.8 nmol/L (182 ng/mL) (reference range, 10.19–58.4 nmol/L [78–447 ng/mL]); and anti–thyroid peroxidase (anti-TPO) antibody 16 IU/mL (<35 IU/mL). Her serum ferritin level was 1.25 nmol/L (560 ng/mL). Her karyotype was 46,XX. The uterine length on ultrasonographic examination was 4.2 cm, and the endometrial thickness was 3.8 mm. Follicles were not seen in either ovary, and there was no evidence of urogenital outflow tract abnormalities. In addition, ovarian blood flow was assessed using color Doppler to document the resistive index (RI) and pulsatility index (PI) at baseline (Table 1). Magnetic resonance imaging of the hypothalamo-pituitary region was unremarkable.

Outcome and Follow-up

After consultation with her treating hematologist, thalidomide was stopped to explore the possible role of thalidomide as a cause of her amenorrhea. After 3 months, she attained menarche. Serum gonadotropin levels normalized, with marked improvement in serum anti-Müllerian hormone (AMH) and estradiol levels (Table 1). A repeat scan of the pelvis detected multiple follicles in the left ovary and one dominant follicle in the right ovary. Endometrial thickness was 8.8 mm, suggesting adequate estrogenization. There was also improvement in ovarian blood flow, as suggested by the reduction in pulsatility index. Her subsequent menstrual cycles were regular. However, following the stoppage of thalidomide, she again became transfusion dependent, requiring frequent blood transfusions to maintain adequate hemoglobin levels.

Table 1. Hormonal and radiological parameters

Parameters	At the time of presentation	1 month after the presentation	3 months after the presentation
LH (mIU/mL)[a]	44.9	32.5	1.24
FSH (mIU/mL)[a]	44.8	39.1	2.38
Estradiol (pmol/L, pg/mL)[a]	220.2 (60.0)	385.4 (105)	403.8 (110)
AMH (pmol/L, ng/mL)[b]	0.22 (0.032)	0.41 (0.058)	13.4 (1.88)
Right ovary: volume (mL)	2	—	4.5
Left ovary: volume (mL)	0.55	—	3.12
Follicular cysts	No cyst in both ovaries	—	One dominant follicle in right Multiple cysts in left
Right ovary:			
RI	0.88	—	1.00
PI	4.33		3.92
Left ovary:			
RI	1.0	—	1.0
PI	6.74		3.69
Endometrial thickness (mm)	3.8	—	8.8

Abbreviations: AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PI, pulsatility index; RI, resistive index.
[a]Measured by Chemiluminescence assay (Immulite® 1000, Siemens).
[b]Measured by Electrochemiluminescence assay (Cobas 6000®, Roche).

Discussion

The absence of menstruation in a woman of reproductive age can be either primary or secondary amenorrhea. Primary amenorrhea in the presence of secondary sexual characteristics is defined by the absence of menarche even after attainment of 15 years of age. Secondary amenorrhea is characterized by the absence of menstruation for more than 3 to 6 months in a previously menstruating woman. It could be either due to abnormalities in the hypothalamo-pituitary-gonadal axis or due to abnormalities of the uterus, including Müllerian agenesis or obstructions in the outflow tract. The most common cause of primary amenorrhea is gonadal dysgenesis, including Turner syndrome. Other disorders include Müllerian agenesis, constitutional delay in puberty, chronic systemic disease, isolated gonadotropin deficiency, hypopituitarism, Cushing syndrome, hypothyroidism, hyperprolactinemia, and any mass in the hypothalamo-pituitary region. Hypothalamo-pituitary dysfunction, possibly due to excessive iron deposition, is the most common etiology of hypogonadism in thalassemia patients and may present with amenorrhea. Studies have demonstrated that gonadotropes are most commonly affected by iron-induced oxidative damage. Iron has not been known to directly affect the ovaries in thalassemia and lead to primary ovarian dysfunction, even in severe forms of thalassemia, even with very high ferritin levels [5].

Individuals with Müllerian agenesis and other utero-vaginal developmental defects usually have normal serum gonadotropins and adequate development of secondary sexual characteristics due to preserved estrogen levels. Our patient had normal secondary sexual characteristics, without features of hyperandrogenism, and had elevated serum gonadotropins, suggesting primary ovarian dysfunction with some circulating serum estrogens. Furthermore, her normal karyotype and ultrasound scan of the pelvis ruled out other possible causes of amenorrhea.

Thalidomide, a glutamic acid derivative, has immunosuppressive effects. The underlying mechanisms of thalidomide-induced ovarian dysfunction are not well understood. Ordi J et al observed a reduced number of follicles and severe atrophy of ovarian tissue on histopathological examination [2]. In vitro studies have demonstrated the possible role of tumor necrosis-α (TNF-α) in the regulation of follicular development, differentiation and apoptosis, and thalidomide is thought to impair follicular maturation by inhibiting TNF-α bioactivity [6]. Thalidomide is also a potent inhibitor of vascular endothelial growth factor (VEGF), which may lead to decreased ovarian blood flow, leading to ovarian senescence [7]. Moreover, the cytoprotective role of thalidomide in chemotherapy-induced ovarian damage is possibly due to a reduction in microvessel

density [8]. In our patient, we also observed a reduction in pulsatility index from baseline, which denotes a decrease in impedance to ovarian blood flow.

Whether the deleterious effect of thalidomide on ovarian function is dose dependent or idiosyncratic remains unknown. Most of the patients who have impaired ovarian function have been prescribed 50 to 100 mg of thalidomide per day. The majority of patients are thought to develop reversible amenorrhea within 6 months of starting therapy (range, 1-42 months). In previous reports, it has been suggested that menstruation usually resumes 3 to 6 months after stopping the drug [9].

Our patient developed thalidomide-induced primary amenorrhea, which has rarely been reported in the literature [10]. She did not have any underlying autoimmune disorders.

Thalidomide may severely impair ovarian function and fertility. It should be used with caution in women of reproductive age.

Learning Points

- The use of thalidomide is associated with ovarian dysfunction.
- Thalidomide may cause reversible ovarian dysfunction leading to amenorrhea.
- The long-term effects of thalidomide on ovarian function are unknown.
- Thalidomide should be used with caution in women of reproductive age.

Acknowledgments

We express our sincere gratitude to Dr. Amritendu Das, MD, Senior Resident, Department of Radiology, Institute of Post Graduate Medical Education & Research for the ultrasound scan.

Contributors

All authors made individual contributions to authorship. A.S., S.G., and P.M. were involved in patient management, diagnosis, and manuscript submission. All authors reviewed and approved the final draft.

Funding

No public or commercial funding.

Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

References

1. Ordi-Ros J, Cortés F, Cucurull E, Mauri M, Buján S, Vilardell M. Thalidomide in the treatment of cutaneous lupus refractory to conventional therapy. *J Rheumatol*. 2000;27(6):1429-1433.
2. Ordi J, Cortes F, Martinez N, Mauri M, De Torres I, Vilardell M. Thalidomide induces amenorrhea in patients with lupus disease. *Arthritis Rheum*. 1998;41(12):2273-2275.
3. Chen JM, Zhu WJ, Liu J, *et al*. Safety and efficacy of thalidomide in patients with transfusion-dependent β-thalassemia: a randomized clinical trial. *Signal Transduct Target Ther*. 2021;6(1):405.
4. Dharia SP, Steinkampf MP, Cater C. Thalidomide-induced amenorrhea: case report and literature review. *Fertil Steril*. 2004;82(2):460-462.
5. Srisukh S, Ongphiphadhanakul B, Bunnag P. Hypogonadism in thalassemia major patients. *J Clin Transl Endocrinol*. 2016;5:42-45.
6. Silva JRV, Lima FEO, Souza ALP, Silva AWB. Interleukin-1β and TNF-α systems in ovarian follicles and their roles during follicular development, oocyte maturation and ovulation. *Zygote*. 2020;28(4):270-277.
7. Roness H, Kalich-Philosoph L, Meirow D. Prevention of chemotherapy-induced ovarian damage: possible roles for hormonal and non-hormonal attenuating agents. *Hum Reprod Update*. 2014;20(5):759-774.
8. Ochalski ME, Orwig KE. Thalidomide reduces ovarian microvasculature and protects ovarian follicles from chemotherapy damage. *Fertil Steril*. 2011;96(3):S33.
9. Pulido-Pérez A, Lázaro-Ochaita P, Suárez-Fernández R. Amenorrhea during thalidomide treatment: an unusual cause of ovarian failure? Amenorrea durante el tratamiento con talidomida: ¿una causa infrecuente de disfunción ovárica?. *Med Clin (Barc)*. 2017;149(3):135-136.
10. Mühlenstedt D, Schwarz M. Gynäkologisch-endokrinologische untersuchungen bei thalidomidgeschädigten Mädchen [gynecological and endocrinological studies of thalidomide-damaged girls]. *Geburtshilfe Frauenheilkd*. 1984;44(4):243-248.