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CASE REPORT

Progressive Oestrogen Deficiency in a Young Woman with 45X/46XX Mosaicism: A Case Report

NIK SUHAILA Z[1], NOOR AZIMAH M[1], ANI AMELIA Z[2]

[1]Department of Family Medicine, [2]Department of Obstetrics and Gynaecology, Faculty of Medicine, Universiti Kebangsaan Malaysia Jalan Yaacob Latiff, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia

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ABSTRAK

Estrogen adalah hormon penting untuk kesihatan wanita. Secara semulajadi, tahap hormon estrogen mula menurun secara beransur-ansur dan menyebabkan gejala yang berkaitan selepas wanita mencapai usia 40 tahun ke atas. Laporan kes ini menggambarkan kekurangan estrogen yang progresif pada seorang wanita muda semenjak usia 19 tahun. Beliau mengalami hipomenorea selama setahun diikuti dengan amenorea dan dikendalikan secara konservatif termasuk diberi cabaran progestogen selama satu tahun. Beliau bertindak balas terhadap rawatan itu pada kali pertama, tetapi mengalami amenorea selepas itu. Beliau dirujuk ke pusat rawatan kami pada usia 22 tahun untuk penilaian lanjut berkaitan masalah kesuburan akibat kekurangan ovari pramatang. Pemeriksaan klinikal menunjukkan seorang wanita muda kurus dengan payudara dan bulu di bahagian ketiak dan kemaluan pada klasifikasi Tanner tahap 3. Ujian darah kali pertama dan ulangan menunjukkan tahap estrogen yang rendah dengan paras gonadotrofin yang berterusan tinggi yang mana menunjukkan keadaan kekurangan ovari primer. Ultrasound pelvis dan urogenital menunjukkan rahim yang kecil dengan lapisan endometrium yang nipis tetapi saiz ovari normal. Beliau didiagnosis dengan Sindrom Turner mozek 45X/46XX berdasarkan ujian kariotip darah. Kekurangan ciri khas Sindrom Turner dalam kes ini telah menyebabkan kelewatan pada penyiasatan dan pengurusan kes. Laporan kes ini bertujuan untuk menekankan pentingnya penilaian menyeluruh pada wanita muda yang mengalami keadaan kekurangan estrogen kronik. Ini akan membolehkan diagnosa dan rawatan awal pada keadaan yang jarang berlaku seperti Sindrom Turner mozek, dan seterusnya dapat mencegah komplikasi.

Kata kunci: 45X/46XX; kekurangan ovari primer; Sindrom Turner mozek

Address for correspondence and reprint requests: Nik Suhaila Zakaria. Department of Family Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia. Tel: +6012-7603240 Email: nsuhailaz@yahoo.com

ABSTRACT

Oestrogen is a vital hormone for woman's health. Naturally, oestrogen hormone level begins to gradually decline leading to related symptoms after the age of 40 years in most women. This case report illustrates a progressive oestrogen deficiency in young woman since she was 19 years old. She was having hypomenorrhea for a year followed with amenorrhoea and was managed conservatively including progestogen challenge for about a year. She responded to the treatment once and remained amenorrhoeic thereafter. She was referred to our centre at 22 years old for further evaluation of premature ovarian insufficiency primarily concerning her fertility. Clinical examination showed a thin young woman with breasts, axillary and pubic hair of Tanner Stage 3. Blood investigation showed low oestrogen level with persistently high gonadotrophins suggestive of primary ovarian insufficiency. The urogenital pelvic ultrasound showed a small thin uterus with normal ovaries. She was diagnosed with Turner Syndrome of 45X/46XX mosaicism based on a blood karyotype test. The lack of typical feature of Turner Syndrome in this case had delayed the initial investigations and management. This case report aimed to highlight on the importance of a comprehensive evaluation in young women presenting with chronic oestrogen deficiency state. This will allow an early diagnosis and treatment of rare condition like mosaic Turner Syndrome and thus, preventing complications.

Keywords: 45X/46XX; mosaic Turner Syndrome; primary ovarian insufficiency

INTRODUCTION

Chronic oestrogen deficiency symptoms like hot flushes, mood change, insomnia and tiredness are less likely to be reported by young women as compared to menstrual abnormalities (ESHRE Guideline Group on POI 2016). The loss of ovarian activity before the age of 40 years that give rise to the symptoms is known as Primary Ovarian Insufficiency or Premature Ovarian Insufficiency (POI) (ESHRE Guideline Group on POI 2016). It is characterised by menstrual disturbance for 4 to 6 months duration with persistently raised gonadotrophins and low oestradiol measured of at least 4 to 6 weeks apart. POI affects 1% of population with lesser prevalence in younger age group (ESHRE Guideline Group on POI 2016). The causes of POI can either be iatrogenic or spontaneous. Iatrogenic POIs are usually due to gynaecological surgical procedure like oophorectomy (i.e. for endometriosis) or treatment regimens for malignant and chronic diseases (i.e. cyclophosphamide for systemic lupus erythematous). The established causes of spontaneous POI include chromosomal or genetic defects, autoimmune disease (thyroiditis and oophoritis), infection (tuberculosis

and Human Immunodeficiency Virus) and environments (smoking, alcohol, and nutrition). However, a significant number (up to 90% in some studies) have unidentified cause which are labelled as idiopathic POI (ESHRE Guideline Group on POI 2016). Even though chromosomal defects account for 10-12% of POI with majority (94%) are X chromosome abnormalities or Turner Syndrome (TS) (ESHRE Guideline Group on POI 2016), the diagnosis of TS is often missed. Typically, women with TS will present with characteristical features of short stature, webbed neck, low hair line, cubitus valgus and primary amenorrhoea (Turner Syndrome Society of United States 2022), which helps in early diagnosis in most cases. This case report is of a mosaic TS with 45X/46XX chromosomes, that presented in a phenotypically normal female at birth and only being diagnosed following a thorough evaluation of her progressive chronic oestrogen deficiency symptoms during her early adulthood. This paper also discussed on the subsequent management of mosaic TS.

CASE REPORT

Ms. A is a 22-year-old female, who was born normally at full term. She grew up as a normal girl with normal developmental milestones and physical growth. She attained thelarche at 12 years old followed by menarche two years later. She had regular menses of 28-30 days cycle with average menstrual flow of seven days. However, she began to have lighter and shorter menstrual flow of about five days at 19 years old and that went on for a year before it completely stopped. She was not sexually active and did not take any medication nor taking any herbal or complementary therapy. She presented to a primary care clinic after missing three menstrual cycles and was treated conservatively with hormonal challenge (medroxyprogesterone) of which she bled for seven days. However, she remained amenorrhoeic following that and failed to respond to the second hormonal challenge given at 3-months follow-up.

Unfortunately, she defaulted follow-up and only sought medical attention again for infertility after one year. She was married for five months and sexually active but had no signs of pregnancy except amenorrhoea. Clinical examination showed a thin short woman with body mass index of 18.2 kg/m^2 (weight 41.5 kg, height 151 cm). Her breasts and pubic hair were graded at Tanner Stage 4 of pubertal maturation. Investigation showed low oestradiol levels of 21 pg/mL, high follicle stimulating hormone (FSH) of 147.2 IU/L and high luteinising hormone (LH) of 54 IU/L. The prolactin, testosterone, thyroid function test and ultrasound pelvis were normal. The FSH and LH were persistently high upon review at 3 months later with reading of 128.5 IU/L and 44 IU/L, respectively. Based on the available investigations thus far, she was diagnosed as having POI and was prescribed combined oral contraceptive (COC) oestrogen-progesterone pills of 21 days duration for three cycles and referred to a tertiary centre for further evaluation.

A thorough review at the tertiary centre revealed she had experienced perimenopausal symptoms like hot flushes, increase temperament, insomnia and tiredness for six months. Notably, her breasts, axillary and pubic hair were graded at Tanner Stage 3 of pubertal maturation in which the breast were small for her age, with sparse pubic and axillary hair. Ultrasound showed a small uterus of 3.5 x 1.7 cm in size with thin endometrium of 3.4 mm. Both ovaries were normal in which right ovary measured 2.2x1.0 cm and left ovary measured 1.9x1.0 cm in size. Blood karyotype test showed she had 45X/46XX chromosomes, a mosaic TS. Upon the diagnosis, she was counselled for fertility status and hormonal therapy using the combined oestrogen-progesterone pills until 50 years old. She was scheduled for a more detail assessments that included bone mineral density test, ultrasound of kidneys, ureters and bladder, echocardiography, audiology test and visual assessment.

DISCUSSION

This case report presented a case of 45X/46XX mosaicism, variant of TS that was only being diagnosed at adulthood. TS is a female genetic disorder, affecting 64 per 100 000 live births (Gravholt et al. 2023). Often the cases are being diagnosed during perinatal or postnatal period and if later, the median age of diagnosis is at 15 years old (Gravholt et al. 2023). Rarely TS cases are being diagnosed after the age of 18 years old (Al Alwan et al. 2014). In terms of the genetic makeup, approximately half of TS have a complete missing of the second X chromosome (monosomy TS, 45X), followed by a partial loss, abnormal second sex chromosome or extra X chromosome in some cells (mosaics TS, 45X/46XX, 45X/46XY, 45X/47XXX) and small percentages have an abnormal arrangement of second sex chromosome (isochromosome TS, 46X,i(Xq) (Al Alwan et al. 2014). Every young woman with non-iatrogenic secondary amenorrhoea should be thoroughly investigated for POI and tested with karyotype or chromosomal test (ESHRE Guideline Group on POI 2016). In addition, it is recommended to proceed with DNA analysis or fluorescent in situ hybridisation (FISH) to detect Y chromosomes mosaicism, that is often missed by the standard karyotyping test even in confirmed cases (Md Zin et al. 2008). Presence of Y chromosome mosaicism is known to be associated with 16-20% risk of developing gonadoblastoma by 30 years old and usually is recommended for prophylactic oophorectomy (Kwon et al. 2017).

The traditional definition of TS implies the presence of physical features such as the characteristic facial appearance with neck webbing and lymphedema, linear growth failure, ovarian insufficiency (pubertal delay), early sensorineural hearing loss, distinctive congenital cardiovascular, skeletal, digital and renal anomalies, a particular neurodevelopmental profile (learning disorder, emotional immaturity and behavioural problems) and presence of hypothyroidism and celiac disease (Gravholt et al. 2017).

The variant TS has lesser characteristic features as compared to monosomy TS but most of them are short in height (Al Alwan et al. 2014). However, the woman in this case report had a normal Malaysian height and slightly taller than the height of classical TS (145 cm) (Tuke et al. 2019). She grew normally into a young woman and had no obvious syndromic features. She attained her thelarche and menarche within the expected age range which masked the TS and thus delayed the diagnosis. It was reported that nearly half of 45X/46XX cases would have thelarche and menarche but only a tenth of monosomy TS cases would have that (Dabrowski et al. 2019). Only 6% of the TS would have regular menstruation with the rest either having primary amenorrhoea, secondary amenorrhoea, or menstrual irregularities (Dabrowski et al. 2019).

Regression of ovarian function usually occurs in early childhood and adolescent while small percentage occurring in adulthood (Al Alwan et al. 2014; ESHRE Guideline Group on POI 2016). The woman had her first sign of oestrogen deficiency at 19 years old with hypomenorrhea, a lighter and shorter menstruation for a year before developing established secondary amenorrhoea. Her initial response to medroxyprogesterone challenge indicates her oestrogen reserve would be of at least 40 pg/ml to enable the bleeding to occur (Dabrowski et al. 2019). However, she failed to respond to the same challenge subsequently. Her ovarian function continued to decline with her oestrogen level recorded at 21 pg/ml. She began to experience perimenopausal symptoms soon after the cessation of COC. Vasomotor symptoms in POI are commonly preceded by menstrual disturbances. Hot flushes and night sweats are the characteristic features of oestrogen deficiency accompanied by urogenital symptoms such as dyspareunia and vaginal dryness, which are usually the most distressing symptoms (ESHRE Guideline Group on POI 2016). The symptoms are intermittent or transient with variable severity that some women may not experience any symptoms at all. Therefore, all the women with secondary amenorrhoea should be asked directly on the vasomotor and urogenital symptoms as most of them are not aware of it (ESHRE Guideline Group on POI 2016). However, some women reported sudden severe symptoms upon cessation of the contraceptive pill (ESHRE Guideline Group on POI 2016) and this is well illustrated in this case. Chronic oestrogen deficiency also leads to regression of breast, pubic hair and axillary hair (Grymowicz et al. 2020) that may be mistakenly labelled as Tanner stage 3 in this case. Being a young adult, she had been compensating well with the changes and symptoms.

Apart from the risk of having TS related anomalies in her heart, kidneys, ears and eyes (Fuchs et al. 2019; Gravholt et al. 2019), the chronic oestrogen deficiency in the young woman can cause arrays of major health issues including premature death, osteoporosis, sexual problems like dyspareunia, depression and cognitive impairment or dementia

(ESHRE Guideline Group on POI 2016; Morris et al. 2020). The mean life-span age for TS is 53±17 years old with cardiovascular event as the main cause of death (Gravholt et al. 2019). Importantly, the low oestrogen level may affect her fertility and lead to the referral to a tertiary centre. The overall fertility rate in TS is of low and less than 10% will conceive within the first two years (Doğer et al. 2015). Almost half of the spontaneous conception ended with pregnancy loss and 11% of the surviving babies had birth defect or serious neonatal illness (ESHRE Guideline Group on POI 2016). Pregnancy in TS, whether spontaneous or assisted, poses a risk of maternal death due to new cardiovascular events like aortic dissection or cardiovascular complications related to their pre-existing heart anomalies (ESHRE Guideline Group on POI 2016). On the other hand, there is also growing evidence that showed mosaic 45X/46XX would have normal reproductive lifespan and birth rate and thus, this information needs to be properly discussed and explained to the woman and her partner (Tuke et al. 2019). A further assessment on her ovarian reserve may be carried out for the decision on the fertility management.

Hormone replacement is the mainstay treatment for oestrogen deficiency in POI. She responded well with the oestrogen-progesterone pills that to be continued until 50 years old, the average age of menopause. It improves the vasomotor symptoms and prevents premature cardiovascular disease and osteoporosis. A balanced diet with adequate calcium (1000-1200 mg/day), vitamin D (800IU/day) intake, weight-bearing exercise, healthy body weight, cessation of smoking and moderate alcohol intake are essential to prevent osteoporosis (ESHRE Guideline Group on POI 2016). Bone mineral density test should be conducted at the diagnosis and repeated every 5 years (Tuke et al. 2019). The hormone replacement should be started early for bone, cardiovascular and neurocognitive protection until at the normal age of physiological menopause (ESHRE Guideline Group on POI 2016).

CONCLUSION

Chronic oestrogen deficiency in previously normal young adult female should prompt the attending physician on the possibility of variant TS like in this case, the rare 45X/46XX mosaicism. All patients with secondary amenorrhoea should be screened for oestrogen deficiency symptoms and sent for karyotype test if indicated. Earlier diagnosis and treatment of chronic oestrogen deficiency state will reduce harmful effects on the women's reproductive, cardiovascular, skeletal, neuro-cognitive and psycho-social function.

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