

Secondary Amenorrhea in a Patient with Common Variable Immunodeficiency

Qian-Hui Zhou^{1,2,3}, Ping Chen^{1,2,3}, Hong Peng^{1,2,3}, Ruo-Yun Ouyang^{1,2,3}, Dai-Qiang Li⁴

¹Department of Respiratory Medicine, The Second Xiangya Hospital, Central South University, 139 Renming Middle Road, Changsha, Hunan 410011, China

²Research Unit of Respiratory Disease, Central South University, 139 Renming Middle Road, Changsha, Hunan 410011, China

³Treatment Center of Respiratory Disease, Central South University, 139 Renming Middle Road, Changsha, Hunan 410011, China

⁴Department of Pathology, The Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, China

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INTRODUCTION

Common variable immunodeficiency (CVID) is a heterogeneous immunodeficiency syndrome characterized by defective antibody formation. Approximately 70–80% of patients are diagnosed based on a previous history of recurrent sinus and lung and gastrointestinal infections. The diagnosis is based on the exclusion of other known causes of humoral defects.^[1] In addition to infections, the coexisting morbidities in CVID include autoimmunity, malignancies, and autoimmune endocrine diseases. We present a case of CVID in which the coexisting morbidities of amenorrhea were associated with a withdrawal bleed following intravenous immunoglobulin (IVIG) treatment.

CASE REPORT

A 24-year-old female was referred to our office for assessment of second amenorrhea for 6 months and recurrent cough and expectoration. She had a history of symptomatic therapy (estrogen for 21 days and progesterone for 7 days) but had no withdrawal bleed. She reported repetitive attacks of sinusitis since childhood. She was 15-year-old at the onset of menarche and had regular periods lasting 4–6 days. Physical examination was normal with the exception of bilateral inspiratory crackles present on lung auscultation.

Laboratory examination revealed hemoglobin: 115 g/L and white blood cell: $3.72 \times 10^9/L$ (neutrophil 85.4%, lymphocyte 7%, and monocyte 6.5%). The levels of IgA, IgG, and IgM were 0.07, 3.17, and 0.09 g/L, respectively, by serum assay. Serum albumin, 64%; alpha-1 globulin, 6.11%; alpha-2 globulin, 8.74%; beta globulin, 14.7%; and gamma globulin, 6.4% levels were detected with protein electrophoresis. Immunocytochemical analysis revealed these levels CD3: 75%, CD4: 54%, CD8: 20%, and CD4/CD8: 2.74. The diagnosis of CVID syndrome was established with immunocytochemical tests.

The gonadotropin-releasing hormone (GnRH) challenge test was as follows: luteinizing hormone (LH): 2.63 mIU/ml, follicle-stimulating hormone (FSH): 7.71 mIU/ml; LH30: 24.45 mIU/ml, FSH30: 19.41 mIU/ml; and LH60: 26.67 mIU/ml, FSH60: 23.81 mIU/ml. The sex hormone levels of LH: 0.66 mIU/ml, FSH: 2.87 mIU/ml, E2: 24.79 pg/ml, prolactin (PRL): 17.48 ng/ml, and T <0.25 ng/ml, respectively, were detected by serum assay. The patient was seronegative for HIV, hepatitis B and C, cytomegalovirus, and Epstein–Barr virus. Immunological connective tissue diseases' workup was negative. Pulmonary function tests showed the following: forced vital capacity (FVC): 2.09 L (68.22%), forced expiratory volume in 1 s (FEV1): 1.33 L (48.91%), total lung capacity: 2.73 L (61.5%), FEV1/FVC%: 65, and the diffusion capacity of lung for carbon monoxide was 49.59% of the predicted value. A chest computed tomography revealed moderate bronchiectasis complicated infections. The size and appearance of ovary, uterus, hypothalamus, and adenohypophysis were normal.

The patient had received regularly IVIG treatment at a dose of 400 mg/kg for 3 days per month and ceftazidime anti-infection therapy, without sequential provision of any sex hormone. She experienced significant clinical improvement of respiratory symptom and maintained a normal level of immunoglobulin (IgA: 0.14 g/L, IgG: 7.18 g/L, and IgM: 0.18 g/L) and sex hormones (LH: 3.12 mIU/ml, FSH: 3.56 mIU/ml, E2: 13.38 pg/ml, PRL: 14.49 ng/ml, and T: 7.43 ng/ml) during 6 months of follow-up. Afterward, the patient received a withdrawal bleed.

Address for correspondence: Dr. Hong Peng,
Department of Respiratory Medicine, The Second Xiangya Hospital
of Central South University, Changsha, Hunan 410011, China
E-Mail: phdiana@126.com

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DISCUSSION

CVID is the most frequent symptomatic primary immunodeficiency. Secondary amenorrhea, which is defined as 3 months of absence of menstruation, occurs in approximately 3–5% of adult women. As reported as the research in 2006, polycystic ovary syndrome, hypothalamic amenorrhea, hyperprolactinemia, and ovarian failure were the most common causes of amenorrhea; in addition, functional hypothalamic amenorrhea (FHA) is responsible for 20–35% of secondary amenorrhea cases.^[2] Among them, hypothalamic amenorrhea is characterized by low levels of FSH, LH, estradiol, and a normal level of prolactin.^[3] The patient's sex hormone levels meet the condition of FHA. In addition, stress, weight loss, strenuous exercise, psychological stress, and systemic chronic illnesses may also be associated with FHA.^[2,3] Our patient suffered from recurrent sinopulmonary infection that caused the body's endocrine disorders and exerted stress on physiologically and mentally to some extent. Hence, the reason of our patient amenorrhea is probably recurrent infection caused by the immunodeficiency and hypogammaglobulinemia.

A cross-sectional study on the menstrual status of 3473 women showed that HIV-positive women experienced more menstrual abnormal compared to the HIV-negative control groups. HIV-positive women with a CD4 count <200, body mass index <20, and who do not take antiretroviral drugs are at the greatest risk.^[4] That is to say, the menstrual cycle is maybe sensitive to the degree of immunodeficiency. Recently, a research on the mechanism of olfactory steroid production in rats found that sex hormone-binding globulin contributed to the rapid effects of olfactory steroids on limbic functions.^[5] These observations led us to question whether sex hormone-binding globulin also plays a role in endometrial proliferation and whether hypogammaglobulinemia reduces the binding of sex hormones with sex hormone-binding globulin. Furthermore, estrogen and progesterone exert their function by binding to specific receptors, which are present within most cell types and, specifically, on several types of immune cells. Low levels of immunoglobulin maybe cut down the binding rate between sex hormone and sex hormones receptor, that is to say, gonadal hormones cannot exert their physiological effects adequately, thereby affecting GnRH synthesis and secretion. These facts also support the hypothesis that CVID-associated B-lymphocyte defects and hypogammaglobulinemia give rise to decrease of sex hormone-binding globulin and sex hormone receptor; consequently, sex hormone cannot effectively promote the periodical change of endometrium [Figure 1].

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts

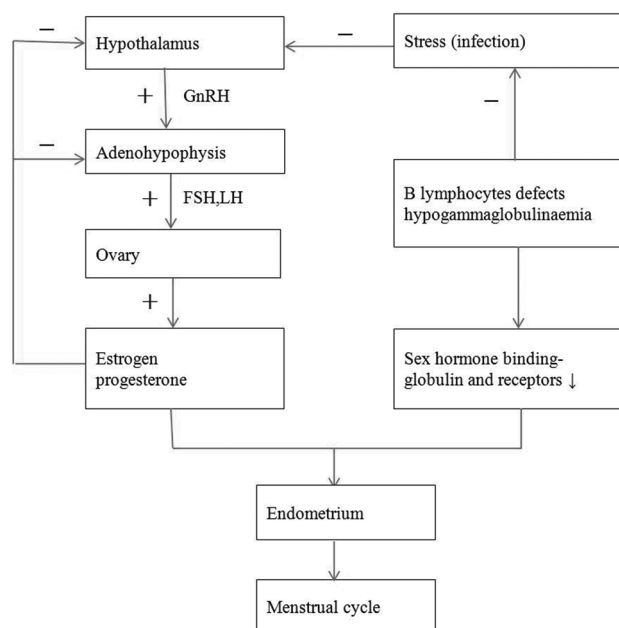


Figure 1: Schematic diagram of sex hormone and periodical change of endometrium.

will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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