A 27-Year-Old Woman Diagnosed as Polycystic Ovary Syndrome Associated with Graves’ Disease

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Abstract

Polycystic ovary syndrome (PCOS) and Graves’ disease are the common causes of menstrual irregularity leading to infertility in women of child-bearing age. A 21-year-old female patient visited us with complaints of oligomenorrhea and hand tremor. She was diagnosed as having PCOS and hyperthyroid Graves’ disease, simultaneously. She had low body weight (BMI: 16.4 kg/m^2), mild hirsutism, and thyrotoxicosis. The patient was treated with anti-thyroid drug and beta-blocker for about two years, and then recovered to normal thyroid function. Although some studies have suggested a connection between PCOS and autoimmune thyroiditis, no study indicated that PCOS is associated with Graves’ disease until now. Here, we describe the first case report of a lean woman with normal insulin sensitivity presenting PCOS and Graves’ disease simultaneously.

Key words: polycystic ovary syndrome, Graves’ disease


Introduction

Graves’ disease, an autoimmune thyroid disease, preferentially occurs in women of child-bearing age. Since Graves’ thyrotoxicosis in women, is frequently associated with a marked change in sex hormones and concurrent menstrual abnormalities, it is difficult to get pregnant or to maintain pregnancy without medication (1).

Polycystic ovary syndrome (PCOS) is a common cause of menstrual abnormalities, anovulation, and infertility in young women, and it is generally associated with hyperandrogenism, visceral obesity, and insulin resistance (2-5).

Although, there are several studies suggesting a relationship between autoimmune diseases including Hashimoto’s thyroiditis and PCOS, to our knowledge, this is the first report of PCOS and Graves’ disease occurring simultaneously (6-10). Here, we report a case of PCOS combined with Graves’ disease showing a lean body figure and normal insulin sensitivity.

Case Report

A 21-year-old female patient visited our hospital with complaints of infertility and hand tremor in 2002. She was admitted for the chief complaints of oligomenorrhea and hand tremor, and diagnosed as PCOS and hyperthyroidism caused by Graves’ disease. After treatment of methimazole for 23 months, she got euthyroid and remission of Graves’ disease. Afterward, she did not visit the hospital for hyperthyroidism. After her marriage in 2007, the patient revisited a local obstetrics clinic due to persistent oligomenorrhea, and not conceiving over 18 months after marriage, hand tremor and palpitation. She was referred to the department

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of endocrinology and metabolism at our hospital under the impression of relapsed Graves’ thyrotoxicosis based on thyroid function test and suspicion of PCOS by uterine ultrasonographic findings.

The patient did not have any particular history other than Graves’ disease and PCOS. Menarche was when she was 13 years old and her cycle was regular. At the age of 18 (2 years prior to the first visit), her menstruation cycle was prolonged and irregular at 8-12 weeks, together with a significantly reduced menstruation volume. She did not drink or smoke and had no family history of autoimmune thyroiditis or other diseases.

At the time of admission, the patient was underweight (height, 160 cm; weight, 42 kg, and body mass index (BMI), 16.4 kg/m²). Blood pressure was 115/66 mmHg, and pulse rate was 106/minute. Moderately enlarged diffuse goiter was palpated in rubbery consistency but exophthalmos was not detected. Hirsutism in the arms and the legs was observed. Nonetheless, other symptoms including alopecia, acne and edema were not detected.

The values for thyroid function tested at the first visit in 2002 were as follows; TSH was 0.02 mIU/L (normal range: 0.34-4.25), free T4 was 3.56 ng/dL (0.8-1.70), autoantibody against TSH-receptor was 4.18 IU/L (0-1.5), and in 99mTc thyroid scan, the uptake ratio was 4.9%. Autoantibodies against thyroglobulin and thyroperoxidase were negative at 34 IU/mL (0-115) and 26 IU/mL (0-34), respectively. The patient was diagnosed as hyperthyroidism caused by Graves’ disease. The symptom was resolved after taking antithyroid drug for 23 months. For the differential diagnosis of oligomenorrhea and hirsutism, a biochemical test was performed. Values are elevated serum androgens, testosterone, 0.93 ng/mL (0.11-0.79); DHEA-S (dehydroepiandrosterone sulfate) 771 ng/dL (35-430) (Table 1). Estradiol (E2) was 45.94 pg/mL (<20-145), progesterone was 0.58 ng/mL (<1.0), prolactin was 16.24 ng/mL (0-20), and 17α-OH-progesterone was 1.11 ng/mL (0.2-1) at the 3rd day of the follicular phase. The LH/FSH ratio was 3.1 (LH 22.02 mIU/mL (2-15), and FSH was 7.04 mIU/mL (3-20). Progesterone withdrawal test was positive, and the polycystic ovary was confirmed by uterine ultrasonography (Fig. 1). Based on these data, the patient was diagnosed as PCOS. At that time, the menstruation cycle was shown to be 8-12 weeks, and the menstruation amount was significantly reduced. During antithyroid drug administration, the menstruation cycle was improved to 6-7 weeks.

At the second visit in 2008, the body weight of patient was similar to one measured at the first visit. Oligomenorrhea and anovulation were observed. In thyroid function test, TSH was 0.01 mIU/L, free T4 was mildly elevated to 2.2 ng/dL. Antibody against TSH receptor was 4.1 IU/L. In technetium 99mTc thyroid scan, the uptake ratio was 5.3%, and both lobes of thyroid were also enlarged (Fig. 2). Autoantibody against thyroperoxidase was 5.36 IU/mL, which was also negative.

The patient was diagnosed relapsed Graves’ hyperthyroidism, and treated with propylthiouracil, 100 mg/day. After 3 months of treatment, TSH was 0.05 mIU/L, free T3 was 3.99 pg/mL, and antibody against TSH receptor was improved to 2.5 IU/L. Nonetheless, oligomenorrhea was still persistent. After resuming euthyroid state, 12-hour fasting blood glucose 91 mg/dL, insulin 7.1 μU/mL, HOMA-IR 1.59, and QUICKI was 0.36. Blood glucose at 2 hours after meal was 87 mg/dL, and glycosylated hemoglobin was 5.4%. Fasting plasma ACTH and cortisol were 37 pg/dL (5-60) and 10.12 μg/dL (5-25 μg/dL), respectively. The LH/FSH ratio was 4.07 (LH 22.02 mIU/mL, FSH 7.04 mIU/mL).

Despite the fact that insulin resistance was not observed in the patient, metformin (500 mg/day) was administered to the patient for 3 months, the oligomenorrhea and testosterone levels were not improved. Rather, gastrointestinal symptoms such as constipation and nausea developed, and thus the medication was terminated. Despite treatment with progesterone, ovulation was not induced. However, ovulation occurred when clomiphene citrate and recombinant FSH was administered.
Table 1. Hormone Study

<table>
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<tr>
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<th>2002.4</th>
<th>2004.3</th>
<th>2008.3</th>
<th>2009.3</th>
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<tr>
<td>Body weight (kg)</td>
<td>39.0</td>
<td>N/A</td>
<td>42.0</td>
<td>41.0</td>
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<tr>
<td>T3 (ng/dL)</td>
<td>298.7</td>
<td>2.95 (freeT3)</td>
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<tr>
<td>Free T4 (ng/dL)</td>
<td>3.56</td>
<td>9.03 (total T4)</td>
<td>2.20</td>
<td>2.79</td>
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<tr>
<td>TSH (mIU/L)</td>
<td>0.02</td>
<td>0.53</td>
<td>0.01</td>
<td>0.02</td>
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<tr>
<td>TSH-R Ab (IU/L)</td>
<td>4.18</td>
<td>0.61</td>
<td>4.10</td>
<td>2.80</td>
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<tr>
<td>Prolactin (ng/mL)</td>
<td>16.24</td>
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<tr>
<td>FSH (mIU/mL)</td>
<td>7.04</td>
<td></td>
<td>6.01</td>
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</tr>
<tr>
<td>LH (mIU/mL)</td>
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<td>24.48</td>
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<tr>
<td>Estradiol (pg/mL)</td>
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<td></td>
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<tr>
<td>Progesterone (ng/mL)</td>
<td>0.58</td>
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<tr>
<td>Testosterone (ng/mL)</td>
<td>0.93</td>
<td></td>
<td>0.84</td>
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<td>DHEA-S (ng/dL)</td>
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<td>17-a-OH-Progesterone (ng/mL)</td>
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<td>Insulin (µU/mL)</td>
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TSH-R Ab: TSH receptor antibody, DHEA-S: dehydroepiandrosterone sulfate

Discussion

We encountered a 27-year-old thin female PCOS patient who was also diagnosed as Graves’ disease with normal glucose tolerance. The patient had hirsutism, the elevated level of androgen, oligomenorrhea, long-term anovulation, and high LH/FSH ratio (>4). The polycystic ovary was detected by ultrasonography, and we confirmed the diagnosis as PCOS (11).

The incidence of PCOS in premenopausal women (20-40 years) is 5-10%. PCOS is a major cause of infertility in women (12). High percentages (50-70%) of PCOS patients accompany with insulin resistance and central obesity. Deterioration of insulin sensitivity, resulting from increased insulin resistance or hyperinsulinemia, suppresses the synthesis of SHBG in the liver, causing the increase of androgen production in the ovary and the adrenal gland. However, how hyperinsulinemia or insulin resistance influences the synthesis of steroids at the cellular level is not clearly elucidated. In addition, Cibula (13) reported that a considerable portion of women with PCOS have insulin sensitivity comparable with healthy controls. According to previous reports, thin female patients with PCOS do not respond to metformin and show no metabolic improvement after treatment of metformin (14, 15). These observations suggested that other mechanisms, rather insulin resistance, might be involved in PCOS development. In the present case, the patient showed low BMI (16.4, 160 cm height, 42 kg weight). In Korea a fasting insulin >12 µU/mL is considered to be insulin resistance (16). In this patient the fasting insulin concentration measured at the time with normal thyroid function was 7.1 µU/mL. In addition, QUICKI was 0.36 and HOMA-IR was 1.59, indicating that the patient shows no insulin resistance according to the Japanese (17) and the Korean population studies (16).

Autoimmune diseases are sometimes associated with early ovary failure or infertility and antibodies for steroid hormone-producing tissues such as the ovary or the adrenal gland and specific enzymes involved in steroid metabolism are also found in these patients suggesting ovarian tissue destruction by autoantibody-induced immune responses. Also in some PCOS patients, a high concentration of antibodies responding to the ovary tissue is detected. In particular, antinuclear antibodies and antibodies against smooth muscles have been occasionally observed (10). Nonetheless, it is still controversial whether autoimmunity is primarily induced during the development of PCOS.

Hashimoto’s thyroiditis, a prevalent autoimmune disease, has been suggested to be generally associated with PCOS (6-8). According to a recent study by Janssen et al (18) comparing 175 PCOS patients and 168 normal women, anti-thyroid antibodies were detected at a high rate in the PCOS group compared to the control group (27% versus 8.3%). A high percentage of the PCOS group showed a typical ultrasonographic finding observed in thyroiditis at low echo compared to control (42.3% versus 6.5%). In addition, a high concentration of serum TSH concentration was detected in the PCOS group (18). They suggested that, because of long-term anovulation in PCOS patients, the reduced level of serum progesterones and relatively elevated estrogen level accelerate the autoimmune response, eventually leading to an increase of Hashimoto’s thyroiditis in patients. In addition, this consequent hypothyroidism, even mild, may induce a vicious deterioration of PCOS by enhancing conversion of androstenedione to testosterone or estradiol, and decreasing metabolism of sex hormones (19). Since PCOS and autoimmune thyroiditis show familial clustering, a common genetic pathway could be involved in the pathological mechanism of these diseases.

Together with Hashimoto’s thyroiditis, Graves’ disease is also a representative chronic autoimmune disease. These two autoimmune diseases can be developed within a family or in an individual at different times (20). Thyrotoxicosis induced by Graves’ disease is associated with menstrual abnormalities including oligomenorrhea or hypomenorrhea. Nonetheless, ovulation normally occurs in most patients, and eventually menstruation cycle and volume are restored to normal when their thyroid function becomes normal. The temporarily elevated SHBG and increased estradiol, testosterone and...
androstenedione cause such menstrual abnormalities (21-24). Considering the not infrequent occurrence of Hashimoto’s thyroiditis in patients with PCOS as shown in previous clinical studies (6-8, 18), the very rare combination of PCOS and Graves’ disease which often develop independently among young women must be interesting. The study of Janssen et al reported that the incidence of chronic autoimmune thyroiditis was 23.9% (47/175) in patients with PCOS, and they also described two subjects with Graves’ disease in PCOS groups (18). There might be an involvement of autoimmunity in the development of PCOS rather than just coincidence of the two diseases. The limited numbers of reports describing the combination of PCOS and Graves’ disease would be due to failure to catch the case in the clinics. To prove this hypothesis, we need to carry out an epidemiological survey of Graves’ disease and PCOS for a large group of Asians in the future.

The present patient presented for oligomenorrhea and hand tremor 6 years previously was definitely diagnosed as both PCOS and Graves’ disease using serological, biochemical, physical examinations and thyroid ultrasonography. The patient has a notably low progestosterone (0.58 ng/mL) and highly elevated estradiol (E2) (45.94 pg/mL). Based on history taking, we suspected the patient to have long-term anovulation. Therefore, reduction of synthesis of immune inhibitory hormones such as progestosterone fails to suppress the immune activation by estrogen, and might lead to induction of Graves’ hyperthyroidism. While the patient was positive for anti-TSH receptor antibody, she was negative for antithyroglobulin antibody or anti-thyroperoxidase antibody. But we are not sure of the existence of other autoantibodies against ovary, adrenal gland and steroidogenic enzymes because we did not perform the serological test for these antibodies. Furthermore, when the patient was administered an anti-thyroid drug, her thyroid function became normal, and the menstruation cycle was also improved to approximately 6 weeks. At that time, sex hormones were not determined, hence, it could not be assessed whether this was associated with the change of the secretion of gonadotropin hormones or sex hormones due to the reduction of free T4. In fact, the oligomenorrhea might have been associated with Graves’ disease. However, regardless of treatment with antithyroid drugs for Graves’ hyperthyroidism for a long time, she has still shown oligomenorrhea and laboratory findings of PCOS. In addition, we cannot exclude the possibility of the involvement of other immune regulatory mechanisms mediated by antithyroid drugs. In the future, further studies are required.

In conclusion, we herein report a case of a 27-year-old female patient diagnosed as both PCOS and Graves’ disease. This case suggests that we need to check goiter and thyroid function tests in women with PCOS. Furthermore, work-ups for ruling out PCOS must be carried out in patients with Graves’ hyperthyroidism when menstrual abnormalities are persistent even after thyroid function recovers to normal. Further studies will be necessary to clarify the association of autoimmunity and PCOS.

The authors state that they have no Conflict of Interest (COI).

References

