Metachronous ovarian mature teratomas with concomitant polycystic ovarian syndrome

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ABSTRACT — A 22 year-old woman presented to our clinic with secondary amenorrhoea, pain of the right adnexal region. At ultrasound, the right ovary presented a multilocular complex mass of 10.4x8.5x7.3 cm enucleated and removed on laparoscopy. The histological diagnosis was mature cystic teratoma. Because of persisting amenorrhoea, the endocrine evaluation performed was consistent with polycystic ovary syndrome (PCOS). Eight months later, two small left ovarian masses were removed by a second laparoscopy and the pathological diagnosis was again mature cystic teratoma. Treatment with myoinositol (MI) 550 mg + D-chiroinositol (DCI) 13.8 mg + folic acid 200 µg twice a day achieved persistent normalization of the endocrine and metabolic values over the 24 months of follow-up. To our knowledge this is an unusual case of multiple and bilateral metachronous ovarian teratomas with a co-existing PCOS.

KEYWORDS
Mature cystic teratoma, metachronous, Hyperandrogenism, Polycystic ovarian syndrome, Myoinositol, D-chiroinositol.

INTRODUCTION

Mature cystic teratoma is the most common germ cell tumor. It accounts for 10% to 20% of all ovarian masses[1]. More than 80% of mature cystic teratomas develop during the reproductive age[2,3]. It can be multiple, with bilaterality reported in 10-15% of cases[4], and metachronous[5,6]. Polycystic Ovary Syndrome (PCOS) is a complex disease characterized by two of these three conditions according to the Rotterdam criteria: hyperandrogenism, chronic anovulation and polycystic ovarian morphology[7]. We report an unusual case of multiple and bilateral metachronous ovarian teratomas with a co-existing PCOS.

CASE REPORT

A 22 year-old woman, para 0, gravida 0, presented to our clinic with secondary amenorrhoea, pain of the right adnexal region and previous diagnosis of PCOS. Oral oestro-progestins were started two months earlier. On clinical examination, she had normal Body Mass Index (BMI = 23.5 Kg/m^2), no hirsutism or acne. Gynecological examination showed an anteverted uterus of normal volume; the left ovary was normal whilst the right ovary was occupied by a mobile mass of approximately 10 cm in diameter. At ultrasound, the left ovary was normal, while the right ovary presented a multilocular complex mass of 10.4x8.5x7.3 cm (Figure 1A). Serum carcinoembryonic antigen, alpha-fetoprotein, CA-125 and β-human chorionic gonadotropin were negative. The mass was enucleated and removed on laparoscopy. Histological examination showed a cyst containing variable proportions of all three germ layers derivatives, consistent with the diagnosis of mature cystic teratoma (Figure 1B). Because of persisting postoperative amenorrhoea, the patient underwent endocrine evaluation. Laboratory results showed elevated LH/FSH

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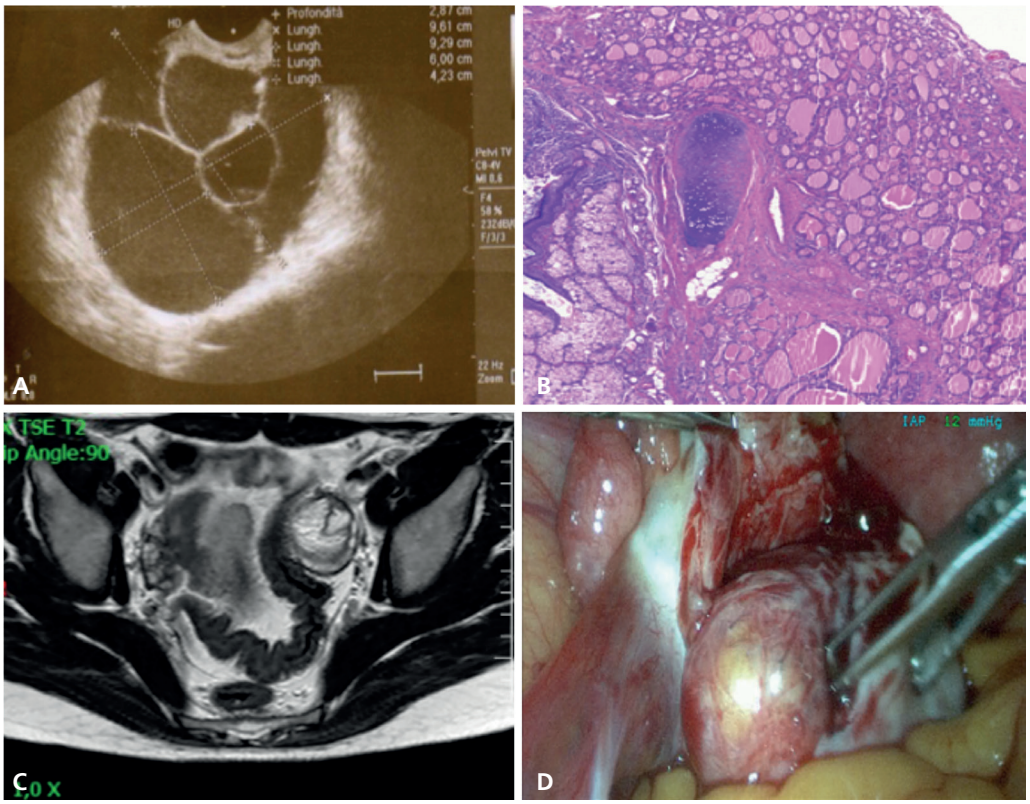

Figure 1. *A,* At ultrasound, the left ovary was normal, whilst the right ovary presented a multilocular complex mass of 10.4x8.5x7.3 cm. *B,* Histological examination showed the presence of all three germ layers derivatives. On the left side, skin with abundant sebaceous glands is visible; on the right side, well-differentiated thyroid tissue predominates. The picture is centered by a nodule of calcified cartilagineous tissue and a small area of adipose tissue. *C,* On MRI, the left annex is increased in volume due to the presence of two expansive rounded formations (3.7x2.2 and 1.4x1.5 cm) with inhomogeneous signal, distinct fat component, modest shared fluid blood ("floating ball"), and small imaging foci of diffusion restriction. *D,* Laparoscopic enucleation and removal of the ovarian masses.

ratio (1.8), total testosterone (85.3 ng/dl; normal range 5-75), dehydroepiandrosterone sulfate (DHEAS) (425 µg/dl; normal range 18-391), androstenedione (5.2 ng/ml; normal range 0-2.83), cortisol (23,5 µg/dl; normal range 6.7-22.6), low sex hormone binding globulins (SHBG) (9.7 nmol/L; normal range 20-85), and severe hyperinsulinemia 475 µIU/ml, two hours oral glucose tolerance test (OGTT), insulin resistance indices (IRI). Nugent test was negative (serum cortisol <1 µg/dl). Computed tomography of the abdomen and pelvis showed normal adrenal glands. Treatment with myoinositol (MI) 550 mg + D-chiroinositol (DCI) 13.8 mg+ folic acid 200 µg, twice a day, was started 2 months after laparoscopic removal of the cystic teratoma, for 6 months; persistent normalization of the endocrine and metabolic values was achieved over the 24 months of follow-up (Figure 2) with a reduction of: LH/FSH ratio from 1.8 to 0.8, total testosterone from 85.3 to 34.8 ng/dl, DHEAS from 425 to 320 µg/dl, androstenedione from 5.2 to 2.0 ng/ml, cortisol from 23.5 to 14.0 µg/dl, and insulinemia from 475 to 63.3 µIU/ml (two hours OGTT, IRI). Eight months later, transvaginal ultrasound showed enlarged ovaries containing over 12 peripheral small follicles (2-9 mm in diameter); the left ovary presented two small areas of 3.7x2.9 cm and 1.4x1.5 cm, both without significant vascular spots by color Doppler imaging. At magnetic resonance imaging, these areas showed distinct fat component, modest shared fluid blood ("floating ball"), and small foci of diffusion restriction (Figure 1C). Laparoscopy was performed, and the two complex masses were enucleated and removed (Figure 1D). Pathological diagnosis was again mature cystic teratoma.

DISCUSSION

Ovarian mature teratoma, a type of germ cell tumor, is composed of mature histologic structures of ectodermal, mesodermal and endodermal origin[8]. It is one of the most common kinds of ovarian tumor, with a frequency of approximately 20%[1]. Although most mature teratomas are asymptomatic, the most common symptoms for this disease are abdominal pain, the presence of an abdominal mass and in very rare cases symptomatology is related to hormonal secretion[4,9]. Only nine cases of androgen-producing ovarian cystic teratomas have been reported[10], and they should be suspected in the case of a rapid onset

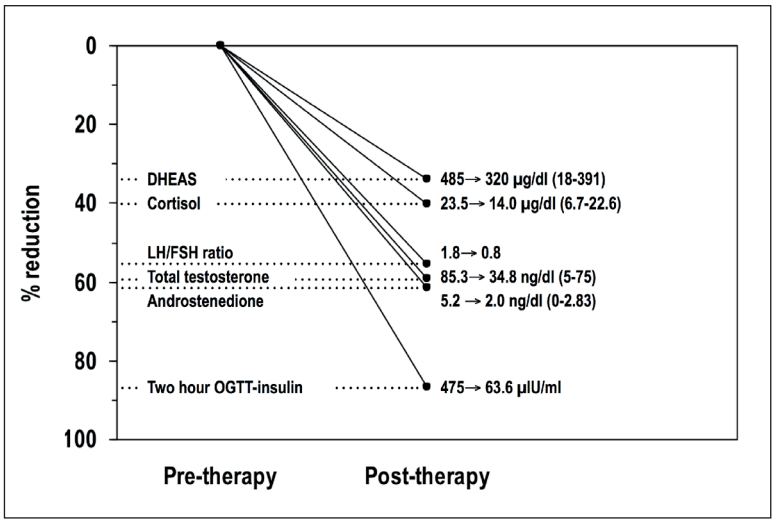

Figure 2. Improvement of serum baseline hormones and oral glucose tolerance test (OGTT)-stimulated insulin values after therapy. The y-axis shows the values % reduction obtained by therapy (values in parenthesis are reference range).

of androgenic symptoms. Androgen-secreting ovarian tumors are rare accounting for less than 0.5% of all ovarian neoplasms; they are more frequent in postmenopausal women and associated with rapidly progressive symptoms of hyperandrogenism, that generally result in various degrees of virilization in around 50% of the cases[11,12]. On the contrary, patients with PCOS present more frequently between the ages of 15-25 years, and the onset of androgenic symptoms is slowly progressive, rarely associated with evidence of virilization or severe hyperandrogenaemia; furthermore the frequent association between PCO, hyperandrogenism, insulin resistance (IR) and hyperinsulinemia, can imply a metabolic syndrome in PCOS[13,14]. Recently, inositols - MI and DCI -, components (in their conjugated form) of cellular membranes crucial for membrane integrity and intracellular signaling, have shown to be an efficient and safe alternative in PCOS management, as both inositol isoforms are able to counteract downstream consequences of IR[15]. In particular, MI induces the translocation of glucose transporter to the cell membrane, thereby enhancing glucose cellular uptake, while DCI stimulates pyruvate dehydrogenase and supports ATP production via the Krebs' cycle[16]. Moreover, DCI glycans specifically stimulate insulin secretion in pancreatic β-cells[17]. Numerous studies have shown that the administration of DCI improves glucose tolerance and insulin sensitivity, reduces androgens and restores ovulation in patients with PCOS[18,19]. Further, MI precursor of DCI, reduces blood levels of insulin and testosterone, restores normal ovarian function, controls metabolic syndrome[20,21]. The combined administration of MI and DCI in a 40 to 1 ratio, which is the physiological plasma ratio, ensures better clinical results in the setting of treatment of PCOS women[15,22]. As shown in Figure 2 the MI+DCI integration determined a reduction between 33% and 62% in endocrine values and of 87% in OGTT-stimulated insulin values.

CONCLUSIONS

Therapy based on MI+DCI (40:1) improves the serum baseline hormones and OGTT-stimulated insulin values in patients with co-existing PCOS in the remaining ovary tissue. To our knowledge this is the first case of multiple and bilateral metachronous ovarian teratomas (two of which localized in the same ovary) with a co-existing PCOS.

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Conflicts of interest:
The Authors declare that there are no conflicts of interest.

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