



SHORT REVIEW

Symptomatic meningioma induced by cross-sex hormone treatment in a male-to-female transsexual

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PALABRAS CLAVE

Terapia hormonal cruzada;
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Estrógenos;

Abstract Transsexualism is defined as a strong conviction of belonging to the opposite sex in individuals without any physical intersex condition. Cross-sex hormone therapy is an important component of medical treatment of transsexuals but it is not exempt from adverse effects.

We report a case of a meningioma in a male-to-female transsexual patient treated with estrogens and cyproterone acetate for the past 4 years. He claimed recently severe headache and visual impairment. Blood tests showed normal results. A contrast-enhanced magnetic resonance imaging (MRI) scan revealed a mass in the tuberculum sellae consistent with a meningioma. Treatment was discontinued and tumor resection was performed. Histologic diagnosis confirmed strongly progesterone receptor-positive and estrogen negative meningioma. After surgery, the patient rejected the possibility of continuing with the treatment of estrogens and cyproterone, and so triptorelin (GnRH agonist) was initiated. At 1-year follow-up the patient's symptoms had ameliorated and a MRI scan revealed no recurrence of the tumor.

This is the third case reported in the literature of a meningioma after treatment with estrogens and cyproterone acetate. We consider extremely important a long-term follow-up observation of male-to-female transsexual undergoing cross-sex hormone therapy in order to detect as soon as possible the adverse effects that can be derived from this therapy.

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Meningioma sintomático inducido por tratamiento hormonal cruzado en un transexual hombre a mujer

Resumen El transexualismo se define como una fuerte convicción de pertenecer al sexo opuesto en aquellos individuos que no tienen ninguna patología intersexual. La terapia hormonal cruzada es un componente fundamental del tratamiento médico de los transexuales, pero debemos tener en cuenta que no está exenta de efectos adversos.

Comunicamos un caso de meningioma en un transexual de hombre-mujer tratado con estrógenos y acetato de ciproterona durante 4 años, que consulta por cefalea y alteraciones

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visuales. Los análisis de sangre eran normales y en la resonancia magnética (RM) se describía una masa en el tubérculo sellar compatible con meningioma. Con estos resultados se interrumpió el tratamiento y se remitió al paciente a cirugía para resección del tumor. La histología tumoral confirmó un meningioma con receptores de progesterona muy positivos y receptores de estrógenos negativos. Tras la cirugía, el paciente desestimó continuar con el tratamiento hormonal cruzado por lo que se comenzó tratamiento con triptorelina (análogo de GnRH). Al año de seguimiento los síntomas habían mejorado significativamente y en la RM de control no había signos de recidiva tumoral.

Este es el tercer caso publicado en la literatura de un meningioma tras tratamiento con estrógenos y progesterona. Consideramos muy importante el seguimiento a largo plazo de los pacientes transexuales que sean sometidos a esta terapia hormonal cruzada para detectar lo antes posible los efectos adversos derivados de la misma.

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Introduction

Transsexualism is defined as a strong conviction of belonging to the opposite sex in individuals without any physical intersex condition, and is a multidimensional phenomenon that requires a multidisciplinary approach.

The treatment of transsexual individuals is a challenge to endocrinologists, who need to work in collaboration with mental health professionals when dealing with such patients. In order to provide relief from the dichotomy between body habits and gender identity, cross-sex hormone therapy has become an important component of medical treatment of transsexuals.

The endocrine society guideline for feminizing treatment in male-to-female transsexuals recommends the use of estrogen together with an anti-androgen to reduce endogenous testosterone levels. Estrogen is usually given orally as conjugated estrogens or 17 β -estradiol, or as transdermal estrogen. Cyproterone acetate, a progestational compound, is one of the most widely used antiandrogenic medication in Europe.¹

Female cross-sex hormone administration can be associated with major adverse effects, of which the most frequent are venous thrombosis, hyperprolactinemia and elevated levels of liver enzymes.¹ Hormone-related tumors such as prolactinomas, breast cancer, prostate cancer and ovarian cancer are other, less prevalent effects. Other hormone tumors, such as meningiomas, are more unusual. As far as we know, this is only the third case report of a male-to-female transsexual patient developing a symptomatic meningioma following sex hormone treatment.^{2,3}

Case report

A 35-year-old male-to-female transsexual patient was referred to the endocrinology department of our hospital with sudden visual disturbance and severe headache. She had been undergoing a feminizing endocrine regimen of estradiol transdermal patches (100 μ g per day) and cyproterone acetate (50 mg twice a day) for the previous four years, without any medical supervision. No sex reassignment surgery had been performed.

Campimetry revealed visual impairment with temporal inferior visual-field defects and optic atrophy of the right eye. Biochemical and hematologic blood tests were normal.

Biochemical and hematologic blood tests were normal prolactin pool, 18 ng/mL (normal range for males: 3.4–19.4 ng/mL); thyroid-stimulating hormone, 1.94 mIU/L (normal range 0.35–4.94 mIU/L); free thyroxine, 1 ng/dL (normal range 0.7–1.5 ng/dL); luteinizing hormone, 0.1 IU/L (normal range 1.0–9.0 IU/L); follicle-stimulating hormone, 0.1 IU/L (normal range 1.0–14.0 IU/L); 17 β -estradiol, 43 pg/mL (normal range 11–44 pg/mL); total testosterone, 8 ng/mL (normal range: 2.8–11 ng/mL); cortisol, 17 μ g/dL (normal range: 4–19 μ g/dL) were analyzed by means of a chemiluminescent microparticle immunoassay (CMIA; Architect Abbott, Abbott Park, IL).

Since there was evident visual impairment, a contrast-enhanced magnetic resonance imaging (MRI) scan was performed and revealed a mass of 26.7 mm \times 25.4 mm \times 16.6 mm in the tuberculum sellae that displaced the optic chiasm backwards and the optic nerves laterally, thus suggesting a meningioma. A CT scan performed two years previously due to a cranioencephalic trauma had not revealed any abnormalities.

Treatment was interrupted and a radical tumor resection was performed without complications.

Postoperative CT scan imaging following the operation was consistent with a right pterional craniotomy with gross total resection of the enhancing portion of the tumor.

The histologic diagnosis confirmed a meningothelial meningioma (benign, WHO classification system grade 1) that was strongly progesterone receptor-positive and estrogen receptor-negative, with a Ki-67 index (cellular marker for proliferation), of 3%.

After surgery, the patient refused to continue with the previous feminizing regimen, and so treatment was initiated with triptorelin (GnRH agonist), an alternative therapeutic option, in order to avoid virilization.

At one-year follow-up the patient's visual impairment and headache had ameliorated and a contrast-enhanced MRI scan confirmed that the tumor had not recurred. However, despite the new treatment, masculine secondary sex characteristics had reappeared.

Discussion

For transsexual patients, acquisition of the secondary sex characteristics of the gender with which they identify is an extremely important aspect of sex reassignment and for this change to come about it is necessary to employ sex steroids. In male-to-female transsexual patients, estrogens are used for feminization, while there are several treatments than can be applied in order to suppress androgenic actions. Cyproterone acetate is commonly employed by European endocrinologists. Other options are spironolactone, finasteride, medroxyprogesterone acetate and long-acting GnRH analogues. As regards progesterone, there is no evidence that its addition to cross-sex hormone treatment contributes to feminization, and it is not usually prescribed due to the many side effects it produces.⁴

Malignancies due to feminizing endocrine regimens in male-to-female transsexuals are not a common adverse effect, although estrogen administration has been related to breast cancer, prostate cancer, ovarian cancer and a few reports of prolactinomas.^{4,5} It has been hypothesized that the role of sex hormones in the development of intracranial meningiomas may explain the increased predominance of these tumors among women, and that the risk of developing one is higher among women with long-term use of contraceptives and postmenopausal women with a history of hormone-replacement therapy.⁶ The evidence suggests that progesterone contributes to the pathogenesis of a meningioma by influencing not only the development but also enlargement of these tumors, since most of these grow during hormonal influx like pregnancy or the luteal phase of the menstrual cycle.⁷ What is more, most meningiomas express functional progesterone receptors, while estrogen receptors have been identified in approximately 10% of cases.

Cyproterone acetate is a synthetic progestin that prevents androgens from binding to the androgen receptor, and has powerful antiandrogen properties. Given that it reduces further body hair growth and contributes to the feminizing effects of estrogens, even after gonadectomy, it is widely used in Europe in cross-sex hormone therapy for male-to-female transsexual patients. The dose required for achieving these effects is 50–100 mg daily. Other indications for this drug are inoperable prostate carcinoma (usually 200–300 mg a day) and severe signs of androgenization in women (androgen-related alopecia, hirsutism, seborrhea or acne).

In 2008, Froelich et al. reported that cyproterone acetate in high doses over long periods of time could promote the development of meningiomas, since they found multiple meningiomas in 9 female patients treated with 50 mg a day of cyproterone acetate for different indications over a period of 10–20 years.⁸ In 2011, Cea-Soriano et al. reported a relationship between hormonal factors and meningiomas in a cohort study of 745 patients diagnosed with this type of tumor. They did not detect a significantly increased risk of meningioma among female users of low-doses of cyproterone acetate (50 mg or less a day), when compared with non-users, whereas said risk was significantly higher among male users of high-dose cyproterone acetate (more than 50 mg daily) when compared with non-users.⁹

Gil et al. in 2011 published the results of a retrospective cohort study performed using Spanish primary care

database. They compared incidence rates of meningiomas in patients exposed to high-dose (50 mg or more a day) and low doses (50 mg or less daily) of cyproterone acetate (considered users) with those in non-exposed patients. They found that the incidence rate was significantly higher among users of high-dose cyproterone than in women receiving low doses and non-users.¹⁰

With all this evidence pointing to a role for progesterone in the development of meningiomas, it is of concern that male-to-female transsexuals are usually treated with progestins.

The first case of meningioma in a male-to-female transsexual was published by Gazzeri et al. in 2007 and concerned a 28-year-old male-to-female transsexual who had been receiving a feminizing endocrine regimen of 100 µg per day of ethinil estradiol and 100 mg per day of cyproterone acetate for the previous 5 years. She developed a giant olfactory-groove meningioma with a histologic diagnosis that revealed a meningothelial meningioma that was negative for estrogen receptors and with a Ki-67 index of 5%.² In 2010 Deipolyi et al. reported another case of a 36-year-old male-to-female transsexual treated with 0.1 mg estradiol patches twice a week over more than 10 years and who developed an occipital meningioma that was strongly progesterone receptor-positive and estrogen receptor-negative.

We believe that the development of the meningioma in our patient was related to her cross-sex hormone treatment with cyproterone acetate, since a CT scan performed prior to her beginning this treatment showed normal results.³

Formal evidence from epidemiological prospective studies is lacking, however all the retrospective studies carried out to date have associated an increased risk of a meningioma with high doses of cyproterone acetate. This leads us to believe that a low dose may be a safer option for treatment of transsexual patients. In fact, we are currently treating patients with 25 mg a day of cyproterone acetate with very good antiandrogenic effects in the absence of any adverse reactions. An other reasonable option is the use of other antiandrogenic drugs such as spironolactone, which has less adverse effects, and to always consider sex reassignment surgery early on.

It is important to point out that this type of tumor does not cause an increase in any biochemical or hormonal values, which means that clinical findings are the ones that will make us suspect a meningioma.

To conclude, we report the third known case of a meningioma in a transsexual patient undergoing a feminizing regimen. The current number of published cases is very low, and so we hope that the present report will serve as guidance to clinicians, who should bear in mind the possibility of this type of complication when treating transsexual patients. Finally, as a result of our experience, we would suggest that hormone treatment be discontinued immediately when a patient receiving a cyproterone acetate regimen develops a meningioma.

Conflicts of interest

The authors have no conflicts of interest to declare.

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