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Genetically burdened transgender man during gender reassignment process with two primary neoplasms: a case report

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ABSTRACT

Transgender is defined as an incongruence between the assigned at birth sex and an experienced gender identity. The biological sex is neither familiar nor acceptable to transgender people. Gender-affirming hormone treatment (GHT) is a multidisciplinary approach aiming to develop and maintain physical characteristics of the desirable sex. The influence of exogenous hormones on the cancer pathogenesis and development is a subject of ceaseless studies and observations. However incomplete statistical and epidemiological data hamper deducing about the risk of cancer among these people. The article describes a case of a transgender female-to-male (FtM) patient during gender transition with two primary neoplasms (endometrial cancer and colon cancer) as well as Lynch syndrome and von Recklinghausen's disease confirmed by next-generation sequencing (NGS).

Key words: transgender, transgender man, cross-sex hormone therapy, Lynch syndrome, von Recklinghausen disease, colon cancer, endometrial cancer

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Introduction

The number of transgender people is increasing. As neoplastic diseases could be also diagnosed in this population, it is necessary to approach the problem of cancers in transgender people properly. We present a case of a transgender male undergoing sex transition with two concomitant primary neoplasms (endometrial cancer and colon cancer), in which DNA (deoxyribonucleic acid) testing using next-generation sequencing (NGS) revealed Lynch's syndrome and von Recklinghausen's disease (VRD).

Case report

A 31-year-old female-to-male transgender patient during the first stage of sex transition (hormone therapy) came to the Oncology Clinic of the University Clinical Center in Katowice in October 2018 after radical surgical treatment for endometrial cancer to have adjuvant treatment introduced. In accordance with the applicable gender criteria and the patient's gender identification, despite the lack of a judicial determination of gender and a non-binary phenotype, the patient was addressed in a male form.

In childhood, the patient was diagnosed with neurofibromatosis type 1 on the basis of clinical symptoms (von Recklinghausen's disease, NF1). The genetically determined disease is caused by *NF-1* suppressor gene mutation and is inherited as autosomal dominant. The physical examination revealed disturbances in the eyes (Lisch nodules of the iris, disorders of the optic nerves), the skeletal (curvature of the spine, short stature) and the nervous system (numerous neurofibromas), as well as the skin (café-au-lait spots, freckles of the inguinal and axillary areas) and additionally characteristic image of brain in magnetic resonance imaging (MRI) with the presence of focal areas of signal intensity (FASI). The patient was under constant ophthalmological and neurological care. He is a technician masseur by profession. A burdened family history suggested NF-1 disease in the father and synchronous breast and ovarian cancer in the maternal grandmother, who died at the age of 50.

At the age of 20, the patient started administrative and medical procedures related to qualification for the FtM gender correction. Having positive opinions from a psychologist, psychiatrist and sexologist, as well as after endocrinological and ophthalmological consultations and the karyotype examination, the patient began the first stage of gender transition in 2010, i.e., testosterone hormone therapy. Until 2015, he had been taking testosterone preparations orally and then in the form of intramuscular injections. In May 2017, the attending physician diagnosed grade 1 microcytic anemia [hemoglobin concentration — 10.7 g/dL, mean erythrocyte volume (MCV) — 65 fL]. For financial reasons, the patient took testosterone preparations irregularly, which resulted in irregular menstruation. The attending physician recognized it as the cause of the anemia and continued the process of gender transition.

In October 2017, he was admitted to the plastic surgery ward to perform the second stage of sex reassignment [gender reassignment surgery (GRS), i.e. mastectomy]. Ultimately, the surgery was not performed due to upper respiratory tract infections, anemia, and coagulation disorders. The patient did not set another date for the procedure.

Subsequently, when the hormone therapy regimen was maintained, menstrual bleeding ceased, but the microcytic anemia gradually worsened and the patient was referred for diagnostics. In March 2018, a colonoscopy was performed in the internal medicine ward, which revealed the presence of multiple large intestine polyps. Numerous samples from the entire colon were taken and based on pathomorphological examination some benign changes were identified. Endoscopic examination of the upper gastrointestinal tract showed no abnormalities. With the diagnosis of adenomatous polyposis of the colon, the patient was referred for a sur-

gical consultation at a reference center. In August 2018, due to a genital hemorrhage, he was hospitalized in the gynecology department, where diagnostic abrasion of the uterine cavity and cervical canal was performed. While waiting for the results of the pathomorphological examination, the patient was scheduled to be admitted to the surgical ward in September 2018 in order to perform additional tests and qualify for restorative proctocolectomy. In an abdominal computed tomography (CT) examination, in addition to the previously identified multiple large intestine polyps, uneven contours of the uterus were described with a thickened endometrium pathologically enhancing after contrast medium administration up to 23 mm. Due to the results of the examination of uterine cavity and cervical scrapings, which revealed endometrial adenocarcinoma, the surgical procedures were stopped and the patient was referred for oncological treatment. Testosterone hormone therapy applied since 2010 in the process of gender reassignment has been suspended.

The patient was qualified for radical treatment due to endometrial cancer. In September 2018 laparoscopic hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy was performed. Pathomorphological examination of the postoperative material revealed the presence of endometrial adenocarcinoma with focal necrosis (*adenocarcinoma endometriales G2 cum necrosi focali*), neoplastic infiltration of the muscular layer 5 × 3 cm and metastasis 2.5 cm in diameter in the right ovary and lymph nodes 21/0+ (stage — pT3aN0M0 = CS IIIA).

Taking the cancer stage into account, the patient was qualified for adjuvant treatment with sequential chemoradiotherapy. From October 2018 to April 2019, systemic treatment was administered at standard doses without complications (6 cycles — carboplatin 400 mg/m² + paclitaxel 175 mg/m² every 21 days), followed by 3D-IMRT teloradiotherapy up to a total dose of 50.4 Gy in 28 fractions. Due to the unfavorable anatomical conditions, it was not possible to carry out brachytherapy after the hormonal therapy. During the treatment, spectral mammography was additionally performed, which showed no pathological lesions in the mammary glands.

Before resuming the interrupted hormone therapy with testosterone in the process of gender reassignment, it was decided to extend the diagnostics to include molecular tests. The patient performed a DNA test using the next-generation sequencing (NGS) method in the commercial program *badamygeny.pl*. The examination detected the Leu1511Pro mutation (c.4532T>C) in one allele of the *NF1* gene, the Ile157Thr mutation (c.470T>C) in one allele of the *CHEK2* gene, and the Arg211Ter mutation (c.631C>T) in one allele of the *PMS2* gene. The disclosed *PMS2* gene mutation — in the context of the previously diagnosed endometrial cancer

— confirmed the diagnosis of Lynch's syndrome (hereditary nonpolyposis colorectal cancer, HNPCC). The consulting clinical geneticist pointed to the extremely rare situation in which one person has two pathogenic, clinically relevant lesions.

Genetic counseling was also provided to the patient's immediate family. The father had a confirmed *NF1* gene mutation, and the mother and younger brother had *PMS2* gene mutation. They are both waiting for diagnostic tests of the digestive tract, and until the publication of the article, neither of them had been diagnosed with cancer.

In September 2019, an endoscopic attempt to remove colon polyps was carried out. Multiple and non-pedunculated laterally spreading type granular (LST-G) and laterally spreading type non-granular (LST-NG) polyps were found in the cecum, ascending colon, hepatic flexure and proximal transverse part. Additionally, in the descending colon and sigmoid colon, single sessile polyps up to 2 mm were visible, and in the sigmoid rectal flexure, a single 20 mm polyp was revealed and removed. The remaining lesions, due to their extensive scope, did not qualify for endoscopic removal. The histopathological examination of the samples taken from the cecum revealed G2 adenocarcinoma.

After diagnostics to assess the disease stage, in November 2019, an extended right hemicolectomy with omentectomy was performed. Despite providing comprehensive information regarding the high risk of multifocal neoplastic lesions in the large intestine, the patient did not consent to the proposed pancolectomy.

The postoperative histopathological report revealed moderately differentiated, partially ulcerated, partially mucinous G2 adenocarcinoma (*adenocarcinoma medio-cere differentiatum G2 exulceratum partim mucinosum*), bifocal tumor located in the cecum and ascending colon, and lymph nodes 17/0+. Two omental and metastatic and one mesenteric metastases were found (disease stage — pT3mN0M1c).

The tumor markers CEA and Ca19-9 remained within the normal range. The patient was qualified for systemic treatment. Chemotherapy was used from January to July 2020. Due to prolonged grade 3 neutropenia after the first cycle of the XELOX regimen (oxaliplatin 130 mg/m², day 1st + capecitabine 1000 mg/m² twice daily — day 1st–14th), the chemotherapy regimen was changed from the second cycle to FOLFOX (oxaliplatin 85 mg/m² day 1st + fluorouracil 400 mg/m² bolus day 1st and 2nd + fluorouracil 600 mg/m² 22-hour infusion on days 1st and 2nd — every 14 days) with prophylactic administration of a short-acting granulocyte colony-stimulating factor (G-CSF). The treatment was complicated twice. First by short-term grade 3 neutropenia and then by grade 1 neuropathy and asthenia. In the third and sixth month of chemotherapy, follow-up CT were

performed, which did not reveal local recurrence and dissemination of the neoplastic disease, and the markers CEA and Ca19-9 remained normal.

Currently, the patient is awaiting a surgical consultation in order to qualify for subcutaneous mastectomy and possible removal of the remaining part of the large intestine. Until now, the previously interrupted testosterone hormone therapy has not been resumed.

Discussion

In everyday life, transsexual people face a lack of social understanding, discrimination, stigma and numerous prejudices (also in the area of health care). For this reason, these people, more often than heteronormative people, avoid contact with a doctor. This translates — among other things — into neglecting periodic tests and screening programs [1, 2]. They are invisible in cancer registries (both in Poland and in the world) [1–3] because the data do not include information about the patient's gender identification and possible gender transition. There is no data on the types and duration of hormone therapies and often information on disease stage and the state of hormone receptors in the case of hormone-sensitive neoplasms. For these reasons, it is impossible to estimate realistically the incidence of neoplasms in the discussed group and the risk of neoplastic diseases related to the conducted hormone therapy [1, 2].

The patient, whose medical history is analyzed in cancer registers and statistics still appears as a woman and is an example of the limitations of the system in this respect. The growing number of transsexual people seeking oncological care prompts a revision of the current, rather indifferent, approach of doctors to the problems of transsexual patients [1–4].

Transgenderism is the lack of compatibility between the biological sex assigned at birth and an experienced gender identity. Biological sex for a transgender person is perceived as alien and unacceptable [5]. Transgender people receive hormone treatment to achieve external sexual characteristics of the desired sex. The influence of exogenous hormones on pathogenesis and development of neoplasms in the discussed population is the subject of research and observation [3].

Moreover, hormone therapy in the process of sex transition is not the only cancer risk factor in this group of patients. Lifestyle (obesity, nicotine, alcohol abuse), carrying specific gene mutations, sexually transmitted viral diseases (e.g. human papillomavirus or immune deficiency) are other potential risk factors for cancer, and surgically reconstructed neo-organs can also be a starting point of a neoplastic process [2].

Undoubtedly, the occurrence of two primary neoplasms in the patient presented above was primarily as-

sociated with the cumulative genetic burden and was not dependent on the hormone therapy used. The risk of developing colorectal cancer associated with *PMS2* gene mutation in Lynch syndrome is up to 21% in women, and the risk of endometrial cancer is 24% compared to 2–3% in the general population [6–8]. A *NFI* gene mutation increases the risk of hematopoietic and lymphatic neoplasms as well as solid cancers, and it is estimated that the lifetime risk may be up to 60% [9, 10]. There has been no evidence to date that exogenous testosterone administration during FtM sex transition increases the risk of endometrial cancer. In studies of postoperative material after removal of the sexual organ, involutinal changes of the uterine body are reported, which are analogous to the changes observed in postmenopausal women [11–13]. Hormone therapy stops menstrual bleeding after a few months, and incidental chronic spotting from the genital tract requires increasing the dose of testosterone [14]. Androgens are physiological precursors of estrogens in the process of peripheral aromatization of testosterone; hence, an increase in serum estrogen levels and the secondary induction of estrogen-dependent tumors in transgender men would be a concern. However, hormone therapy aimed at maintaining testosterone levels within the physiological limits of cisgender men (men with the same gender assigned at birth and gender identity) does not increase serum estrogen levels [15].

Oncologists should consider the possibility of breast cancer in transgender people. The risk of cancer in FtM patients after mastectomy is lower, and in the absence of mastectomy is similar compared to the population of cisgender women [16]. Before an elective mastectomy, it is suggested to perform a mammography, especially in people with a family history, and the postoperative material should undergo pathomorphological examination in order to exclude cancer [17]. Transgender women and transgender men who have not undergone mastectomy should have a mammogram every 2 years from the age of 50, if the duration of hormone therapy is longer than 5 years [16]. On the other hand, in transgender men after mastectomy, the decision to screen for breast cancer should be made individually. In this group, breast cancer may develop in the glandular tissue, which is usually preserved to achieve a good esthetic result. In individuals with a burdened family history, ultrasound examinations or magnetic resonance imaging of the remaining breast gland should be considered [16–18].

Summary

The occurrence of two primary neoplasms in the presented transgender FtM patient was mainly related to the cumulative genetic burden, and not to administered hormone therapy. Incomplete data on the occurrence, treatment and recurrence of neoplastic diseases in the population of transgender people do not allow for an

unequivocal assessment of hormone therapy safety. A transsexual patient with cancer requires the participation of a sexologist, endocrinologist and psychologist as part of multidisciplinary cancer care.

Conflict of interest

The authors declare no conflict of interest.

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