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Testicular cancer in two brothers of a quadruplet: a case report and a review of literature

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Introduction. Testicular cancer and a multiple birth are both rare events, and the risk of testicular cancer is increased in twins. In Lithuania, only five quadruplets have been recorded since the middle of the 20th century. In this report, we present two rare events in one family: testicular cancer in two brothers of a quadruplet (three brothers and a sister).

Case description. Both patients were diagnosed at 21 years of age and died within two years from the diagnosis despite treatment. The third symptomless brother did not have testicular pathology. We also review the risk factors associated with testicular cancer, and the proposed hypotheses how a multiple birth results in an increased risk. The most consistent risk factors for testicular cancer are cryptorchidism, prior history of testicular cancer, and a positive familial history. According to different studies, the risk of testicular cancer in twins is higher from 22% to 30%, compared to the general population.

Conclusions. To our knowledge, we have presented the first case of testicular teratoblastoma in brothers of a quadruplet.

Keywords: testicular cancer, quadruplet, multiple birth, risk factors

INTRODUCTION

Accounting for approximately 1% of all male cancers, testicular cancer is a rare malignancy worldwide (1). The incidence of testicular cancer in Lithuania is one of the lowest in Northern Europe – 2.1 per 100,000 in Lithuania and 15.4 per 100,000 in Denmark reported for the same period (2). Multiple births are rare events; of these, triplets and quadruplets are even rarer. In Lithuania (3 million residents according to the 2011 census) only five quadruplet births have been recorded since the Second World War.

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In this report, we present two rare coincident events in one family – testicular cancer in two brothers of a quadruplet.

CASE PRESENTATION

In 2014, an article about the lives of a quadruplet (tree brothers and a sister), born in Lithuania in 1969, appeared in the press. By that time, two of the brothers were deceased after unsuccessful treatment of testicular cancer more than 20 years ago. The two brothers were diagnosed with testicular cancer during their military service. The third symptomless brother did not have any testicular pathology.

Upon discovering this information in the press, we reviewed the patient database in the National

Cancer Registry and found both cases. One of the brothers was diagnosed with right testicular teratoblastoma, staged T3N3M0 in January 1991, and died in December 1991, after unsuccessful treatment with resection and radiotherapy, followed by palliative care and analgesic treatment. The second brother – with right testicular teratoblastoma with metastases in the lymph nodes and lungs, staged T3N3M1 in December 1990 – died in July 1992. Similarly, the treatment consisted of orchiectomy and polychemotherapy and radiotherapy to the region of affected lymph nodes.

It is not clear whether the affected brothers were hetero- or monozygotic. Since one of the brothers claimed that people found it difficult to distinguish between them, monozygoticity is possible.

DISCUSSION

Although testicular cancer is a rare diagnosis, it is the most common cancer among young (15–40-year-old) men and its incidence has been increasing steadily in Europe since 1920 (2–4). At least 90% of testicular tumors belong to the group of germ cell tumors (GCTs), which are classified according to the 2004 classification of the World Health Organization (WHO). Race is one of the most important etiologic factors in the development of GCTs: white men in Western industrialized countries show the highest rates of incidence (5). Non-seminoma is somewhat more aggressive and usually appears in men in their 20s, as compared to seminoma, which usually appears in men in their 30s [6].

In general, the most consistent risk factors for testicular cancer are cryptorchidism, a prior history of testicular cancer, and a positive familial history. Other risk factors are small birth weight, small gestational age, inguinal hernia, twinning (7), adult height, and a low BMI (8, 9) – possibly as proxies of the birth-cohort effect. Somewhat less relevant are professional (firefighting, aircraft maintenance) and environmental (organochloride pesticides, marijuana use) risk factors (10, 11).

According to different studies, the risk of testicular cancer in twins is higher from 22% to 30%, compared to the general population (7, 12). There is no definite answer whether the effect is genetic or environmental, e. g., through shared intrauterine environment.

It has been proposed that 25–33% of all testicular GCT patients have a genetic predisposition (13). Familial aggregations of testicular GCT have been well described, suggesting the existence of a hereditary GCT subset. Approximately 1.4% of newly diagnosed testicular GCT patients report a positive family history of testicular GCT. Sons have four- to six-fold, while siblings of testicular GCT patients have eight- to ten-fold increase in testicular GCT risk, respectively. Segregation analyses suggest an autosomal recessive mode of inheritance (14).

Testicular cancer is hypothesized to be associated with etiologic factors that operate *in utero* or in early childhood. Swerdlow et al. (15) originally found dizygotic twins to carry a reliably higher risk than monozygotic. In a systematic review of seven studies, Neale et al. (12) (and Cook et al. (7) in an updated alternative review) did not find enough support for different testicular cancer risk in dizygotic compared to monozygotic or like-sex twins. This hints to the importance of environmental factors, namely, the environment *in utero*. Testicular cancer is also associated with other developmental flaws (cryptorchidism, hypospadias, inguinal hernia), and could have common pathogenetic elements with genital abnormalities. One of the suggested culprits for the increased risk in twins is the imbalanced maternal hormones. A twin (especially dizygotic) pregnancy results in a higher level of maternal estrogens, thereby increased fetal exposure, and imbalance of estrogens and androgens.

Gene expression analyses of a number of testicular GCT and pre-invasive samples provide additional support for tumour initiation *in utero* through a pre-invasive stage of intratubular germ cell neoplasia unclassified (IGCNU) [16–20]. Men with IGCNU, which is observed already at the fetal stage, will develop testicular GCT within 5 years at the rate of 50% (21, 22). Despite the differential profiles for different histological subtypes (seminomas versus non-seminomas), gene expression analyses suggest the differentiation from IGCNU to seminomas or embryonal carcinomas with embryonic or extra-embryonic differentiation for the latter. In most cases, the gain of chromosome arm 12p is associated with IGCNU and is suggested to be necessary for progression (23, 24). Genes associated with malignant transformation,

proliferation, stemness and pluripotency (KRAS, CCND2, STELLA, NANOG) are located within this region, often amplified in testicular GCT (25, 26). Gains of chromosomes 7, 8, 21, and X are reported in testicular GCT as well (23, 25, 27). Further genome-wide association studies identified six more loci implicated in testicular GCT, also suggesting the initiation stage *in utero* [28–30]. Nevertheless, mutations in fibroblast growth factor receptor 3 gene FGFR3 and HRAS, found exclusively in spermatocytic seminomas, suggest a different tumorogenesis pathway associated with the accumulation of mutations during the adult life span (31).

Epidemiological studies indicate that familial testicular cancer risk has both heritable and environmental components. The joint European population study showed that sons and brothers of testicular cancer patients are at a higher risk of developing this cancer at an age close to the age at diagnosis of their relatives (32). A high familial risk between brothers of similar age compared with those with a large age difference may be an indication of environmental contribution to the familial aggregation (33). The environmental effect was also demonstrated in a study of migrants in Sweden: sons of both Finnish (low-risk area) and Danish (high-risk area) immigrants adopted the Swedish risk profile instead of having the one of their parents (34). In the nationwide Swedish Family-Cancer Database study, testicular cancer has also been reported as the one with the highest proportion of childhood-shared environmental effects (35). These results suggest that environmental factors during childhood and adolescence strongly impact the risk of testicular cancer.

Recent studies led to an improved understanding of the parameters involved in the earliest pathogenetic steps of human germ cells tumors, particularly the seminomas and non-seminomas. Analysis of genome copy alterations and SNPs (single-nucleotide polymorphism) associated with testicular GCT suggested a few biochemical pathways of the testicular GCT development (24). Alterations of primordial germ cells (PGCs) migration, apoptosis and alterations during sex determination at embryogenesis are suggested to contribute to testicular GCT development (28–30). On the other hand, regulation of these biochemical pathways is micro-environment dependent (36–39) therefore testicular GCT development may be initiated by micro-environment changes *in utero* without any genetic alterations. In the case of a disturbed gonadal physiology, either due to the germ cell itself or the micro-environment, the maturation of embryonic germ cells can be blocked during a specific window of sensitization, resulting in carcinoma in situ or gonadoblastoma, the precursors of seminomas and nonseminomas. The level of testicularization of the gonad determines the histological composition of the precursor (40).

CONCLUSIONS

Testicular cancer risk is increased in twins, but the rarity of each of these conditions makes the association difficult to study. Genetic and environmental factors, including the etiologic factors that operate *in utero*, could possibly explain the increased risk, but the exact mechanism remains to be elucidated. Due to extreme rarity, testicular cancer in multiple births other than twins has not been reported yet. To our knowledge, we have presented the first case of testicular teratoblastoma in two brothers of a quadruplet.

Conflict of interests: the authors declare that they have no conflict of interests.

Informed consent: written informed consent for publication of the family case was provided by the living brother of the quadruplet. Additional informed consent was obtained for the identifying information that is included in this article.

Ethical approval: all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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DVIEJŲ KETVERTUKO BROLIŲ SĖKLIDŽIŲ VĖŽYS: ATVEJO APRAŠYMAS IR LITERATŪROS APŽVALGA

Santrauka

Įžanga. Sėklidžių vėžys ir daugiavaisis nėštumas – du reti įvykiai. Sėklidžių vėžio rizika dvyniams yra padidėjusi. Lietuvoje nuo XX a. vidurio ketvertuko gimimas stebėtas tik 5 kartus. Šiame atvejo aprašyme pristatome du vienoje šeimoje nutikusius retus įvykius – dviejų brolių iš ketvertuko (trijų brolių ir sesers) sėklidžių vėžį.

Atvejo aprašymas. Abiems pacientams sėklidžių vėžys buvo diagnozuotas 21-erių metų amžiaus ir, nepaisant gydymo, abu pacientai mirė praėjus dvejiems metams nuo diagnozės nustatymo. Trečiam broliui sėklidžių patologija nustatyta nebuvo. Šiame straipsnyje taip pat apžvelgiame rizikos veiksnius, siejamus su sėklidžių vėžiu, bei hipotezes, kodėl didesnę riziką lemia daugiavaisis nėštumas. Nuosekliausiai įrodyti sėklidžių vėžio rizikos veiksniai – kriptorchidizmas, jau buvęs sėklidžių vėžys ir teigiama šeiminė anamnezė. Įvairių studijų duomenimis, sėklidžių vėžio rizika dvyniams yra 22–30 % didesnė nei bendrai populiacijai.

Išvados. Mūsų žiniomis, tai pirmasis aprašytas dviejų brolių iš ketvertuko sėklidžių teratoblastomos atvejis.

Raktažodžiai: sėklidžių vėžys, ketvertukas, daugiavaisis nėštumas, rizikos veiksniai