

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

Agnė Ulytė¹,

Albertas Ulys²,

Kęstutis Sužiedėlis²,

Aušvydas Patašius²,

Giedrė Smailytė^{1,2}

¹ Faculty of Medicine, Vilnius University,
Vilnius, Lithuania

² National Cancer Institute,
Vilnius, Lithuania

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.

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 (three 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

Correspondence to: Agnė Ulytė, Birutės St. 38-2, LT-08114 Vilnius, Lithuania. E-mail: agne.ulyte1@gmail.com

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 tumorigenesis 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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References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015; 136: E359–6.

2. Richiardi L, Bellocco R, Adami HO, Torrang A, Barlow L, Hakulinen T, Rahu M, Stengrevics A, Storm H, Tretli S, Kurtinaitis J, Tyczynski JE, Akre O. Testicular cancer incidence in eight northern European countries: secular and recent trends. *Cancer Epidemiol Biomarkers Prev.* 2004; 13: 2157–66.
3. Trabert B, Chen J, Devesa SS, Bray F, McGlynn KA. International patterns and trends in testicular cancer incidence, overall and by histologic subtype, 1973–2007. *Andrology.* 2015; 3: 4–12.
4. Bergstrom R, Adami HO, Mohnner M, Zatonski W, Storm H, Ekblom A, Tretli S, Teppo L, Akre O, Hakulinen T. Increase in testicular cancer incidence in six European countries: a birth cohort phenomenon. *J Natl Cancer Inst.* 1996; 88: 727–3.
5. Mikuz G. Update on the pathology of testicular tumors. *Anal Quant Cytopathol Histopathol.* 2015; 37: 75–85.
6. Motzer RJ, Feldman DR and Bosl GJ. Testicular Cancer. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J (eds.). *Harrison's Principles of Internal Medicine*, 19th edition. McGraw-Hill Education, New York, 2015.
7. Cook MB, Akre O, Forman D, Madigan MP, Richiardi L, McGlynn KA. A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer – experiences of the son. *Int J Epidemiol.* 2010; 39: 1605–18.
8. Richiardi L, Vizzini L, Pastore G, Segnan N, Gillio-Tos A, Fiano V, Grasso C, Ciuffreda L, Lista P, Pearce N, Merletti F. Lifetime growth and risk of testicular cancer. *IJC.* 2014; 135: 695–701.
9. Lerro CC, McGlynn KA, Cook MB. A systematic review and meta-analysis of the relationship between body size and testicular cancer. *Br J Cancer.* 2010; 103: 1467–74.
10. McGlynn KA, Trabert B. Adolescent and adult risk factors for testicular cancer. *Nat Rev Urol.* 2012; 9: 339–49.
11. Lacson JC, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK. Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. *Cancer.* 2012; 118: 5374–83.
12. Neale RE, Carriere P, Murphy MF, Baade PD. Testicular cancer in twins: a meta-analysis. *Br J Cancer.* 2008; 98: 171–3.
13. Nicholson PW, Harland SJ. Inheritance and testicular cancer. *Br J Cancer.* 1995; 71: 421–6.
14. Greene MH, Kratz CP, Mai PL, Mueller C, Peters JA, Bratslavsky G, Ling A, Choyke PM, Premkumar A, Bracci J, Watkins RJ, McMaster ML, Korde LA. Familial testicular germ cell tumors in adults: 2010 summary of genetic risk factors and clinical phenotype. *Endocr Relat Cancer.* 2010; 17: R109–21.
15. Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochie NE. Risks of breast and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet.* 1997; 350: 1723–8.
16. Skotheim RI, Monni O, Mousses S, Fossa SD, Kallioniemi OP, Lothe RA, Kallioniemi A. New insights into testicular germ cell tumorigenesis from gene expression profiling. *Cancer Res.* 2002; 62: 2359–64.
17. Sperger JM, Chen X, Draper JS, Antosiewicz JE, Chon CH, Jones SB, Brooks JD, Andrews PW, Brown PO, Thomson JA. Gene expression patterns in human embryonic stem cells and human pluripotent germ cell tumors. *Proc Natl Acad Sci USA.* 2003; 100: 13350–5.
18. Almstrup K, Hoei-Hansen CE, Nielsen JE, Wirkner U, Ansorge W, Skakkebaek NE, Rajpert-De Meyts E, Leffers H. Genome-wide gene expression profiling of testicular carcinoma in situ progression into overt tumours. *Br J Cancer.* 2005; 92: 1934–41.
19. Korkola JE, Houldsworth J, Dobrzynski D, Olshen AB, Reuter VE, Bosl GJ, Chaganti RS. Gene expression-based classification of nonseminomatous male germ cell tumors. *Oncogene.* 2005; 24: 5101–7.
20. Port M, Schmelz HU, Stockinger M, Sparwasser C, Albers P, Pottek T, Abend M. Gene expression profiling in seminoma and nonseminoma. *J Clin Oncol.* 2005; 23: 58–69.
21. Jacobsen GK, Henriques UV. A fetal testis with intratubular germ cell neoplasia (ITGCN). *Mod Pathol.* 1992; 5: 547–9.
22. Oosterhuis JW, Looijenga LH. Testicular germ-cell tumours in a broader perspective. *Nat Rev Cancer.* 2005; 5: 210–22.

23. Atkin NB, Baker MC. Specific chromosome change, i(12p), in testicular tumours? *Lancet*. 1982; 2: 1349.
24. Gilbert D, Rapley E, Shipley J. Testicular germ cell tumours: predisposition genes and the male germ cell niche. *Nat Rev Cancer*. 2011; 11: 278–88.
25. Zafarana G, Grygalewicz B, Gillis AJ, Vissers LE, van de Vliet W, van Gurp RJ, Stoop H, Debiec-Rychter M, Oosterhuis JW, van Kessel AG, Schoenmakers EF, Looijenga LH, Veltman JA. 12p-amplicon structure analysis in testicular germ cell tumors of adolescents and adults by array CGH. *Oncogene*. 2003; 22: 7695–701.
26. Clark AT, Rodriguez RT, Bodnar MS, Abeyta MJ, Cedars MI, Turek PJ, Firpo MT, Reijo Pera RA. Human STELLAR, NANOG, and GDF3 genes are expressed in pluripotent cells and map to chromosome 12p13, a hotspot for teratocarcinoma. *Stem Cells*. 2004; 22: 169–79.
27. Henegariu O, Vance GH, Heiber D, Pera M, Heerema NA. Triple-color FISH analysis of 12p amplification in testicular germ-cell tumors using 12p band-specific painting probes. *J Mol Med (Berl)*. 1998; 76: 648–55.
28. Kanetsky PA, Mitra N, Vardhanabhuti S, Li M, Vaughn DJ, Letrero R, Ciosek SL, Doody DR, Smith LM, Weaver J, Albano A, Chen C, Starr JR, Rader DJ, Godwin AK, Reilly MP, Hakonarson H, Schwartz SM, Nathanson KL. Common variation in KITLG and at 5q31.3 predisposes to testicular germ cell cancer. *Nat Genet*. 2009; 41: 811–5.
29. Rapley EA, Turnbull C, Al Olama AA, Dermizakis ET, Linger R, Huddart RA, Renwick A, Hughes D, Hines S, Seal S, Morrison J, Nsengimana J, Deloukas P, UK Testicular Cancer Collaboration, Rahman N, Bishop DT, Easton DF, Stratton MR. A genome-wide association study of testicular germ cell tumor. *Nat Genet*. 2009; 41: 807–10.
30. Turnbull C, Rapley EA, Seal S, Pernet D, Renwick A, Hughes D, Ricketts M, Linger R, Nsengimana J, Deloukas P, Huddart RA, Bishop DT, Easton DF, Stratton MR, Rahman N, UK Testicular Cancer Collaboration. Variants near DMRT1, TERT and ATF7IP are associated with testicular germ cell cancer. *Nat Genet*. 2009; 42: 604–7.
31. Goriely A, Hansen RM, Taylor IB, Olesen IA, Jacobsen GK, McGowan SJ, Pfeifer SP, McVean GA, Rajpert-De Meyts E, Wilkie AO. Activating mutations in FGFR3 and HRAS reveal a shared genetic origin for congenital disorders and testicular tumors. *Nat Genet*. 2009; 41: 1247–52.
32. Kharazmi E, Hemminki K, Pukkala E, Sundquist K, Tryggvadottir L, Tretli S, Olsen JH, Fallah M. Cancer risk in relatives of testicular cancer patients by histology type and age at diagnosis: a joint study from five Nordic countries. *Eur Urol*. 2015; 68: 283–9.
33. Hemminki K, Li X. Familial risk in testicular cancer as a clue to a heritable and environmental aetiology. *Br J Cancer*. 2004; 90: 1765–70.
34. Hemminki K, Li X. Cancer risk in Nordic immigrants and their offspring in Sweden. *Eur J Cancer*. 2002; 38: 2428–34.
35. Czene K, Lichtenstein P, Hemminki K. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish Family-Cancer Database. *Int J Cancer*. 2002; 99: 260–6.
36. Smith CA, McClive PJ, Western PS, Reed KJ, Sinclair AH. Conservation of a sex-determining gene. *Nature*. 1999; 402: 601–2.
37. Molyneaux K, Wylie C. Primordial germ cell migration. *Int J Dev Biol*. 2004; 48: 537–44.
38. Runyan C, Schaible K, Molyneaux K, Wang Z, Levin L, Wylie C. Steel factor controls midline cell death of primordial germ cells and is essential for their normal proliferation and migration. *Development*. 2006; 133: 4861–9.
39. Farini D, La Sala G, Tedesco M, De Felici M. Chemoattractant action and molecular signaling pathways of Kit ligand on mouse primordial germ cells. *Dev Biol*. 2007; 306: 572–83.
40. Looijenga LH. Testicular germ cell tumors. *Pediatr Endocrinol Rev Suppl*. 2014; 2: 251–62.

Agnė Ulytė, Albetras Ulys, Kęstutis Sužiedėlis,
Aušvydas Patašius, Giedrė Smailytė

**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 am-

žiaus 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