Cryptorchidism and testicular neoplasia

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ABSTRACT

Objectives: Traditionally there is a concern about the possibility of developing testicular tumors as a consequence of undescended testis. This study was conducted to investigate the correlation between testicular tumors and undescended testis.

Methods: Medical records of all patients with testicular germ cell cancer were seen and examined at the Princess Basma Teaching Hospital, Jordan University of Science and Technology, Irbid, Jordan, between 1990 and 2000 (group 1) for any evidence of undescended testis. All males with undescended testis attending the infertility clinic during the period 1999-2001 (group 2) were re-evaluated for any evidence of testicular tumors. The operative records of all patients who had surgery for undescended testis during the past 30 years (group 3) were reviewed and the patients were contacted to see if any of them developed testicular tumor as expected.

Results: Forty-four patients with testicular germinal cell tumors; mean age at diagnosis were 32.6 years (range 20-50) were identified. All patients had unilateral involvement and none of them were found to have tumors in undescended testis. The tumor was in the scrotum in all patients. None of the 117 infertile patients with undescended testis had clinical or ultrasonic evidence of testicular tumors. Two thousand nine hundred and nineteen patients had an operation for undescended testicle in the past 30 years, average of 97.3 operations annually. Median age at surgery for undescended testis was 7.7 years (range 2-29 years). None of the 2071 patients who were traceable developed testicular tumor.

Conclusion: We found no evidence to support that patients with undescended testis are at a higher risk than the general population to develop testicular cancer.

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Testicular neoplasms (TN) constitute approximately 1% of all male tumors. It is the most common registered malignancy among males aged 25-40 years.[1,2] Cryptorchidism (undescended testis [UDT]), on the other hand, is more common and seen in approximately 5-6% of full-term babies and 25% of preterm infants.[3,4] The etiology of TN is not clear with multifactorial origin. Undescended testis has long been incriminated as both a risk factor and a cause for the development of TN. Risk of 3-10 times of developing testicular cancer, particularly pure seminoma, has been implicated.[5,6] This heightened and overemphasized concern leads many authors to recommend life-long follow-up, repeated scrotal ultrasound (US) and post-pubertal orchidectomy for patients with UDT.[7,8] This phobia and terror were even more clearly expressed by recommending orchidectomy in patients presenting after the age of 2 years with this anomaly.[8] This long-standing belief has not been consistent with our clinical observation and practice. In this paper, the association between TN and UDT will be discussed.

Methods. Our data includes the study of 3 groups of patients. The first group includes all patients with documented pathological diagnosis of testicular germ cell tumor (seminoma and non-seminoma). These patients were treated in the Princess Basma Teaching Hospital, Irbid, Northern Jordan, during the period between January 1990 and December 2000. This

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hospital is a tertiary referral center for people living in Irbid, Jordan. Radical orchidectomy specimens were processed and registered by the Pathology Department, Faculty of Medicine, Jordan University of Science and Technology. The clinical notes, pathological classification and follow-up notes were retrospectively analyzed with the objective of finding any occurrence of contralateral tumor in the remaining testis or defining a history of testicular maldescent and its management. Follow-up for the other testis was mainly achieved by clinical examination. Further radiological and pathological studies were carried out in the presence of positive clinical findings. Simultaneous contralateral testicular biopsy was not carried out in our institution due to ethical and sociocultural reasons. The 2nd group includes all males with UDT attending the infertility clinic during the period 1999-2001. They were re-evaluated by scrotal examination and ultrasonography. The 3rd group was comprised of all patients who underwent surgery for UDT at the same hospital during the last 30 years. Their names were obtained from the operative records. The occurrence of TN in this group was sought by phone and mail communication of index cases and their associates, contacting all relevant clinics and departments in Jordan such as urology, pediatric surgery, pathology and oncology and consulting with the Jordanian National Cancer Registry statistics. These measures did not include recruitment of any patient for clinical re-evaluation.

Results. There were 44 patients (group 1) with TN. Their ages ranged from 20-50 years (mean=32.6). All were unilateral with 32 seminoma, 9 nonseminoma and 3 of the mixed type. None of these tumors developed in an UDT. Two out of 44 (4.5%) developed contralateral TN in a normally descended testis (one teratocarcinoma, one seminoma) during an average follow-up period of 6 years and 3 months. None of the patients had evidence of congenital anomalies, Down's syndrome or ambiguous genitalia. The estimated total population of Irbid during 1998 was 848,340 inhabitants (439,185 males and 409,155 females) constituting approximately 17.8% of the total Jordanian population (51.8% males).[9] Our hospital serves approximately 65% of this population (551,421; 285,470 males and 265,951 females). The estimated total population of Jordan during the same year was 4,755,750 (2,486,800 males and 2,268,950 females).[9] During 1998 only 26 cases of testicular cancer were diagnosed in Jordan giving an incidence rate of 0.55/100,000 population (1.04/100,000 males).[9] The incidence rate drawn from our data for Irbid was slightly higher at 0.73/1,000,000 population (1.4/100,000 males), indicating that we were not missing cases of testicular cancer in Irbid. One hundred and seventeen infertile males with UDT attended the infertility clinic during the period 1999-2001 (group 2). These were selected from a total number of 1900 infertile patients with an average age of 25.6 years (range 18-43). The average age at surgery was 5.6 years (range 2-27) and follow-up period ranged from 1-10 years (mean=6.9 years). None of these 117 patients had clinical or ultrasonic evidence of TN. No pathological studies were conducted. Group 3 consisted of 2919 patients who underwent an operation for UDT during the last 30 years. The total number of primary operations was 3065 with an average of 102.2 operations per year. Their median age at surgery was 7.7 years (range 2-29 years). **Table 1** illustrates some of the basic features of this group of patients. Orchidopexy in our institution is performed in the classical 2 incision, subdartos pouch technique. Testicular fixation was achieved by tunical non-absorbable sutures. Orchidectomy was carried out for patients with small atrophic, some abdominal and few postpubertal testicles. The number of testis removed in patients more than 14 years of age was only 29. This is due to sociocultural reluctance coupled with the refusal of patients and their parents. No pathological evidence of TN including carcinoma in situ (CIS) was reported in these removed testicles. Out of the 2919 patients, 2379 (81.5%) patients had an average immediate follow-up period of 15.2 months and there was no clinical evidence of TN. At that time scrotal US was not carried out for these cases. From this 3rd group, 2071 (70.9%) were traceable using the above measures. There was not a single case of TN reported or documented among these patients.

Table 1 - Basic features of group 3.

Characteristics	n	(%)
Site		
Abdominal	151	(5.2)
Canalicular	2768	
Laterality		
Unilateral	2627	
Bilateral	292	(10)
Operation		
Orchidopexy	2649	
Orchidectomy	416	(13.6)

Discussion. Several risk factors have been linked to testicular cancer: exogenous hormone exposure, bleeding and threatened miscarriage, maternal cigarette smoking, pre-term birth, first births among mothers below the age of 24 years at conception, history of undescended testis, gonadal dysgenesis, infertility, previously diagnosed testicular tumor and family history of the disease (genetic predisposition).[10-13] The occurrence of more than 50% of these tumors remains unexplained. The weight of UDT as a risk factor or a cause of TN have not been matched in epidemiological studies. The age-standardized incidence of germ cell cancer is 1.3-7.8 per 100,000,[14] while that of UDT ranges

between 0.3-30% among all age groups.[15] There are also no prospective controlled data in the literature to reveal the association of isolated forms of UDT with TN. Other studies have pointed out a possible shared etiological mechanism for both UDT and TN. Hormonal disturbance, abnormal development and genetic background were all suggested as contributing to the development of both conditions.[10,11,13,16,17] In this setting, a clear distinction between an effect and a cause is very difficult. Attempt at referring to all clinical, radiological and pathological studies relating to both UDT and TN is exhausting. In the following discussion, we will try to highlight some of these aspects and show the complexity of this relationship. Cortes et al[18] studied 1335 cryptorchid boys with 1638 biopsies at surgery. Various forms of germinal cell abnormalities were seen as early as 18 months of age. Significant disturbances in semen parameters with consequent infertility were also reported in their follow-up. Testicular neoplasm, however, was not seen at all in boys with isolated intra-canalicular UDT (0/1185). Five percent of patients with abdominal testis, ambiguous genitalia or abnormal karyotype had an associated testicular tumor. Hadziselimovic et al[19] studied both cryptorchid boys and infertile men in relation to pathology. Higher number of seminomas was detected among infertile patients with abnormal spermiograms (6/1121 versus 4/2528). Three out of the 4 seminomas in cryptorchid boys occurred in abdominal testicles. Persistent gonocytes or primordial germ cells in UDT were present in 0.5% of boys.[19] In our review, none of the studies showed evidence of reduction or elimination of the risk of developing TN in UDT as regards to correction or age at surgery. This fact is well established by Berkmen and Alagol[8] who studied 876 patients with germinal cell tumor during the period 1984-1996. Twenty-five of them had evidence of UDT (2.9%), the majority was seminomas, 3/25 had an associated persistent Mullerian duct syndrome and 11 developed in abdominal testicles. This risk was neither altered by orchidopexy nor by variation of age at surgery.[8] This implies that the mere correction of testicular position or altering the period of exposure is not necessarily preventive. Indirect evidence of weaker association between UDT and TN has long been overlooked in infertility and pathological studies. Engeler et al[20] followed-up 15 patients with a history of early orchidopexy and positive placental-like alkaline phosphatase antibodies as a marker for intratubular germ cell neoplasia of the unclassified type for more than 2 decades. None developed testicular cancer. The impact of UDT on fertility potential was significant.[20] Vinardi et al[21] reviewed 57 men (average age 19 years) with UDT treated by hormonal or surgical manipulation during childhood for an average of 13.3 years. None of these patients developed TN.[21] The occurrence of non-germ testicular tumors in UDT has not been remarkable. Leydig cell tumor and teratoma are among some of the cases reported in the literature.[22,23] Patients with Down's syndrome have a higher incidence of cryptorchidism. In a study reviewing 36 cases of TN with Down's syndrome, only 17.1% of them were shown to have UDT. This is a much lower percentage considering the high association with UDT.[24] Common genetic mechanism may underline both gonadal development and TN in patients with Down's syndrome.[25] The relationship between CIS (as a precursor for TN), testicular micro-calcification (microlithiasis, TM) and commonly incriminated risk factors was extensively reviewed by Holm et al.[26] In this review, the association of UDT and TM with CIS was not impressive and conflicting. They showed that CIS is, in fact, more common in patients with a history of TN or present with ambiguous genitalia. They criticized the lack of biopsy confirmation in some studies and advised a better policy for radiological (US) follow-up. Carcinoma in situ is found in less than 1% of the normal population, which corresponds to the life-time risk of testicular cancer in males. This pathology is observed in 25% of patients with ambiguous genitalia, 5% contralateral testis of patients with testicular cancer and 3% in UDT. Carcinoma in situ cells are probably derived from primordial germ cells since birth independent of testicular location.[27] Huff et al[28] analyzed 767 boys with unilateral UDT who underwent orchidopexy and bilateral testicular biopsy at the same time. Their data revealed disturbed germinal cell maturation with no evidence of CIS or testicular cancer. Long-term ultrasonic evaluation (no biopsy) of 75 surgically corrected UDT's failed to reveal any case of TN.[29] Testicular micro-calcification is a relatively common finding by scrotal US. Its relationship with UDT has been documented.[26,29,30] Testicular micro-calcification occurs in more than 5% of healthy young men and it is not considered, generally, pre-malignant.[26,31,32] Nicolas et al[30] followed-up 63/202 patients with a history of orchidopexy during childhood for an average of 9 years by scrotal ultrasonography (no biopsy), 9.52% of them had evidence of TM with no suspicion of TN.[30] Scrotal ultrasonography, in addition to clinical, biochemical and pathological assessment is helpful in following-up and screening patients for TN. It is, however, operator-dependent, needs standardization and can be misleading if not combined with histopathological confirmation. Ward et al[33] raised an interesting issue in their ultrasonic evaluation of post-pubertal corrected UDT's. They found a significant number of patients with tunica albuginea calcification and hypo-echogenic cysts. These findings were attributed to the use of sutures (especially catgut) in testicular fixation. Their follow-up data for more than 14 years did not show any evidence of parenchymal ultrasonographic abnormalities suggestive of TN. No biopsy studies were contemplated.[33] Our data included a large number of patients. In all patients with TN, infertile men with history of UDT and operated cryptorchid boys, no clue was found incriminating UDT as a risk factor for TN. The follow-up period for all groups was fairly long. At the end of this argument, we would like to highlight

some of the inherent shortcomings in our study! These include lack of control, loss of completeness, retrospectivity and absence of both radiological and pathological studies. It is however fair to say that our observation is remarkable and cannot be ignored. We were able to note that the engagement between UDT and TN is ill-justified. This discussion is not only academic, but also has significant management implications. It helps in "brain-storming" and paves the way for finding a possible common etiological mechanism for both TN and its commonly incriminated risk factors. We plea for the medical professionals to look carefully at our data and literature overview in a critical manner. More meticulous attention to CIS and intra-abdominal testis is required. Our interest in this issue will further be enriched by starting a prospective, controlled and comprehensive evaluation of patients with UDT for the coming 10 years. In this proposed study, the faults seen in our current data and literature will be avoided. Epidemiological, clinical, radiological, biochemical and histopathological features will be included. We believe that testicular germ cell tumors originate from a common abnormal gonocyte, which in turn persists from birth as a result of genetic or environmental factors. The contribution of those 2 factors varies among different populations. This makes epidemiological features indispensable for both specific and comparative analysis.

In conclusion, UDT has long been considered as a risk factor or a cause for TN. Our data and literature did not support this engagement. More critical analysis and "fair trial" need to be considered. We feel that both conditions are victims of a common insult.

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