Testicular cancer patterns in Tunisian men : Diagnosis problems, pathological types and prognosis. About 41 patients

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Les aspects du cancer testiculaire chez l'homme tunisien:
Problèmes diagnostics, types pathologiques et pronostic
À propos de 41 patients

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RÉSUMÉ

But : Analyser l'incidence, les aspects diagnostics, le grade histologique, le stade, et la survie du cancer du testicule (CaT) chez les hommes Tunisiens.

Méthodes: Nous avons étudié tous les patients porteurs d'un CaT confirmé histologiquement et traités au CHU La Rabta entre 1991 et 2010. Ces données ont été analysés: âge au moment du diagnostic, l'année du diagnostic, les symptômes cliniques, le stade au moment du diagnostic, le type histologique, la conduite thérapeutique et de la survie.

Résultats: L'incidence du CaT chez les Tunisiens est faible; nous avons colligés seulement 41 cas sur une période de 20 ans avec une incidence moyenne de 2 nouveaux cas par an. Le pic d'incidence se trouve entre 30 et 49 ans. La Tumeur testiculaire était le principal motif de consultation chez 25 patients. 58,5% des tumeurs étaient du côté droit et 39% étaient du côté gauche. La tumeur était bilatérale dans un seul cas. L'intervalle moyen entre l'apparition des symptômes et la présentation était de 16,5 mois (1-120). La plupart des patients étaient aux stades T2 et T3 (63,4% et 26,8% respectivement). Le traitement a consisté en une orchidectomie radicale chez tous les patients associée à une chimiothérapie à base de cisplatine et la radiothérapie dans respectivement 11 et 12 patients (association chez 5 patients). Un patient avec une tumeur sur un testicule intra abdominale a eu une orchidectomie par laparotomie. Les types histologiques les plus fréquents étaient les séminomes (n = 20) et les tumeurs à cellules germinales mixtes (n = 8). Trois patients sont décédés dans les 48 mois, tandis que la moitié a été perdue au suivi.

Conclusion : L'incidence des CaTs en Tunisie reste faible. Le diagnostic et le traitement tardifs posent un vrai problème de conduite thérapeutique. Une meilleure éducation sanitaire en particulier avec l'auto-palpation des testicules est indispensable.

Mots-clés

Testicule, Cancer, Incidence, Epidémiologie, Cryptorchidie, Orchidectomie, Mortalité, Tunisie.

SUMMARY

Aim: To analyze the testicular cancer (TCa) incidence, diagnosis aspects, pathologic grade, stage, and survival in Tunisian men.

Methods: We studied all patients who had histopathologically confirmed TCa treated in La Rabta University-Hospital between 1991 and 2010. Baseline demographic data included age at diagnosis, year of diagnosis, clinical symptoms, stage at diagnosis, histologic type, management strategies and survival were analyzed.

Results: The incidence of TCa among Tunisians is very low; we collected only 41 cases over a period of 20 years with an average incidence of 2 new cases per year.

Peak age incidence was 30-49 years. Testicular swelling was the principal complaint in 25 patients. 58.5% of tumours were right-sided and 39% were left-sided. There was bilateral involvement in only one case. The mean interval between onset of symptoms and presentation was 16.5 months (1-120). Most patients presented at stages T2 and T3 (63.4% and 26.8% respectively). Treatment consisted of radical orchidectomy in all patients and cisplatin-based chemotherapy and radiotherapy in respectively 11 and 12 patients (association in 5 patients).

One patient with a tumour in an intra-abdominal testis underwent laparotomy. The most common histological types were seminomas (n=20) and mixed germ cell (n=8). Three patients died within 48 months, while half were lost to follow-up.

Conclusions: The incidence of TCas in Tunisia remains low. Late presentation and treatment are major challenges to management.

Better health funding and education regarding testicular self-examination is essential.

Key-words

Testicular, Cancer, Incidence, Epidemiology, Cryptorchidism, Orchiectomy, Mortality, Tunisia.

Testicular cancer (TCa) accounted for 1.1% of all cancers in males in the year 2000 (1). The reported annual incidence rate was 5.2 per 100,000 men for all races during 1996 to 2000 (2). Interestingly, this incidence has shown a remarkable geographical variation worldwide. The highest incidence rates (7-10 per 100,000 men) are found in Norway, Denmark, and the UK (3, 4). In contrast, this rate can be as low as 1 per 100,000 men in some countries in Africa and Asia, such as Egypt and Singapore (3, 4). Although it is reported as rare in Tunisia, few are known about this cancer in Tunisian men.

To evaluate our real situation, we review all TCas examined in the departments of Urology and Histopathology in the Rabta University-Teaching Hospital, Tunis, Tunisia. We analyzed the clinical presentation, risk factors, histopathologic variants, outcome and challenges in the management of TCa in Tunisia. We, also, determined whether the stage at presentation and the histologic type were associated with the discrepancies in observed survival.

PATIENTS AND METHODS

This is a retrospective study including all patients who had histopathologically confirmed TCa between 1991 and 2010 (20 years). During this period 41 patients were managed for TCa. Diagnosis of TCa was made on clinical examination (palpable testicular mass with or without abdominal mass), scrotal-abdominal ultrasonography, computed tomography scanning (CTScan), chest radiograph and evaluation of tumour markers (beta-human chorionic gonadotrophin (ßHCG), alpha-fetoprotein (αFP) and lactate dehydrogenase (LDH)). Definitive diagnosis was based on histopathological analysis of the operative specimen after orchiectomy in all cases. Clinical staging was according to the TNM staging system (TNM classification for testicular cancer (5). TCas were classified according to the World health Organization classification system 2004 (6). Patients were excluded if the stage at presentation or histologic type was unknown. Those without pathological confirmation of testicular cancer were also excluded.

Data on age at presentation, year of diagnosis, clinical features, laterality, radiological and biological investigations, stage, histologic type, treatment given, special management problems, outcome and survival were obtained for each individual. We defined loss to follow-up as any patient not seen for up to 12 months after presentation and treatment.

Statistical analysis:

The survival time was defined as the interval between the date of diagnosis and either death or last consultation. Overall survival, stage-adjusted survival, and stage and histologic type-adjusted survival were examined using the Kaplan-Meier method. Data analysis was done by means of SPSS software, version 15 (SPSS, Chicago, IL, USA).

RESULTS

Between 1991 and 2010, during 20 years, there were a total number of 41 cases of TCa diagnosed in the Rabta University Hospital with an average of 2 new cases per year. We managed about 10 new cases every 5 years. TCA incidence remains stable: 12 patients between 1991 and 1995 and 9 patients between 2006 and 2010. There were 1347 male malignancies in this period making TCa to account for 3% of all urological cancers in men. TCa was the 5th urinary malignancy in our department after bladder, prostate, renal and upper urinary tract cancers. The mean age was 42.8 ± 7.2 years (18-83). About half of cases occurred in the 3rd and 4th decades as shown in table I. Only 6 patients had a history of cryptorchidism (14.6%) and 4 had a history of scrotal trauma (9.7%). No patient had TCa in his first-degree relatives. Twenty-five patients (61%) presented with intra-scrotal testicular masses. Other clinical presentations include: scrotal pain (n=11), fever (n=2), lumbar pain (n=1), hydrocele (n=1), primary infertility with gynaecomastia (n=1) and digestive trouble (n=1). The mean duration of symptoms before presentation was 16.5 months (range 1-120 months).

Table 1: Age incidence of testicular tumors

Age (yrs)	< 20	[20-30[	[30-40[	[40-50[	[50-60[	[60-70[	≥ 70
Number	2	6	11	9	6	4	3

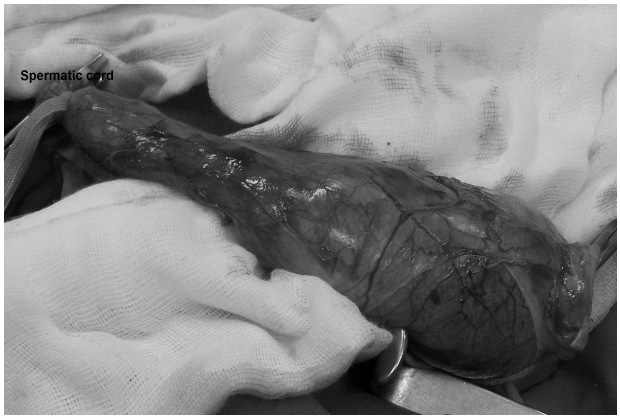
The first suspected diagnosis was TCa (n=34), orchiepididymitis (n=5), urinary tuberculosis (n=1) and hydrocele in one case. Physical examination revealed intra scrotal testicular mass in 39 cases, inguinal mass in one case and a hypotrophic testis with a nodule in one case. Three patients had poor general health status. Twenty-four of the tumours were on the right side (58.5%) while 16 (39%) were left-sided. There was bilateral involvement in only one case. Cervical non-supra clavicular or supra clavicular lymph node involvement was not seen in any of our patients.

Following the history and physical examination, chest radiograph and CTScan were done. In the absence of CT imaging, we relied on abdominal ultrasonography to detect gross retroperitoneal lymph node involvement and hepatic metastasis (5 cases).

CT Scan was available in 24 cases and was normal in 12 of them. Retroperitoneal lymph node involvement was seen in 10 patients with unilateral upper urinary tract dilation in two cases. Pulmonary metastases occurred in 3 and liver metastases in 7 patients. Renal and suprarenal metastasis was suspected in one patient each. Thrombosis of superior vena cava was reported in 2 patients.

Biological data were available in only 27 patients. αFP was elevated in 6 patients, ßHCG was elevated in 4 patients, both αFP and ßHCG were negative in 15 patients and LDH was elevated in 6 cases. Carcinoembryonic antigen level was normal in two patients. The patient with gynaecomastia had a hyperprolactinaemia.According to the available data, most patients presented at stages T2 and T3 (63.4% and 26,8% respectively). Radical orchiectomy was performed in all patients, through an inguinal approach in 40 patients (Figure 1) and by laparotomy in one patient (TCa on an intra-abdominal testis).

Figure 1 : Macroscopic view of an orchiectomy specimen.



Because of large volume of TCas in almost all cases (>2 cm in 40 patients), we didn't suggest tumor spearing surgery to any of these patients. Germ cell tumors were found in 31 men (75.6%). Of these, pure seminoma occurred in 46.3% of the patients, mixed germ cell tumours in 19.5% and Teratomas in 2.4 %. Tumors of lymphoid tissues were seen in four patients (10 %) (Table 2). The most frequent variants of TCas (Seminoma and Mixed germ cell) have their highest incidence respectively between 40-60 years (47.3 %) and 20-40 years (62.5 %) of age respectively.

Table 2: Patient characteristics: Histologic type

Histologic type	Patient's number	%
Germ cell tumours:	31	75.6 %
Seminoma:	19	46.3 %
Non-seminoma:	12	29.3%
Mixed germ cell	08	19.5%
Yolk sac tumour	02	4.8%
Teratoma	01	2.4%
Spermatocytic seminoma	01	2.4 %
Sex cord/ gonadal stromal tumours:	10	24.4 %
Lymphoma	04	10 %
Plasmacytoma	01	2.4%
Leydig cell tumor	01	2.4%
Andoblastoma	01	2.4%
Rhabdomyosarcoma	01	2.4%
Leiomyosarcoma	01	2.4%
Spermatocytic carcinoma	01	2.4 %

Radical orchiectomy was the only treatment and good enough in 7 patients (because of very poor general health condition in one patient). Radical orchiectomy with radiotherapy was the most common treatment combination, and was done in 7 (17%) patients (24-25 Gy). It was focused on the lymph node or recurrence areas (1 case: 30 Gy). Radical orchiectomy and cisplatin-based chemotherapy was done in 6 (14.6%) patients. Association of radio and chemotherapy was indicated in 5 cases. Retroperitoneal lymph node dissection was indicated in two cases but one patient refused consent after being informed of the ejaculatory difficulty that might follow. The reason behind the refusal was fear of infertility, which has strong cultural and social consequences in Arab countries.

According to prognostic-based staging system for metastatic germ cell cancer (IGCCCG), 12 patients with seminomas (63%) have good prognosis although only 4 patients with non-seminomas (33%) have good prognosis.

Five patients failed to receive the recommended radiotherapy/chemotherapy and re-presented in a moribund condition. Twenty patients were lost to follow-up as early as 3 months after our primary intervention. The mean duration of follow-up for the others was 48.6 months (12-156). Only 6 patients were available for follow-up and well after 5 years. Three patients died within 48 months of presentation and initial treatment response; two of them had metastases at presentation.

DISCUSSION

TCa is still a relatively rare disease (7), accounting for 0.5-2% of male neoplasms (8), with 3-6 new cases/occurring per 100,000 males/per year in Western society (1, 2). It is nonetheless the most common malignancy in young men aged between 15 and 35 years in most populations globally (3, 9-13). In our series, about half of patients were at their 3rd and 4th decades of life (Table 1). This is higher than most previous African reports (7, 14, 15).

According to the register of north Tunisia, TCa is the 4th urological neoplam after bladder, prostate and kidney cancers. Over a 5-year period (1999-2003), 66 cases were reported, in a population of 4.5 million people (16). It represents 0.4% of cancers and 2.4% of urological cancers in men (16). Its incidence is 0.6 new cases / 100 000 Tunisian males per year. So far, we don't have enough data about this pathology in Tunisia. Recent studies have documented an increase in TCa incidence over the past 40 yr (17, 18) in the majority of the industrialized countries but surprising differences in incidence rates are seen between neighboring countries (19). The highest incidence rates were reported in predominantly caucasian regions, particularly Europe (6.7-7.8%) and North America (5.1%), Southern Europe and Central America displayed slightly lower incidences of 4.2% and 3.7%, respectively, whereas the lowest incidence rates were in Asia (0.5-1.5%) and Africa (0.2-0.7%) (20-22). TCas still remain relatively rare among native African men compared to whites (7). This low incidence has remained unchanged over the past half a century (7). The incidence of TCa in our institute is low and seems to be stable (≥ 2 cases /yr) over these last two decades.

The exact cause of TCa is unknown. We do, however, know that

there are several risk factors linked to TCa. Amongst the more common causative factors suggested are a prior history of cryptorchidism or undescended testis (23-25), the role of sedentary lifestyle and lack of exercise and even the high socioeconomic status (26-28). Six of our patients had a history of cryptorchidism and 4 had a history of scrotal trauma. Other potential explanations include familial history of TCas among 1st grade relatives (father /brothers), infertility, prenatal estrogen exposure, dietary intake composition, smoking habits, increasing environmental pollution occupational hazards, and birthplace (11, 23, 29-33).

In the present series, right sided involvement was predominant while there was only one case of bilateral TCa. Similar data were previously reported (20).

The symptoms of TCa are not specific. They are usually discovered after the patient or his sexual partner palpates an abnormal intrascrotal mass or painless enlargement of the testis (10, 34). Reduction in testis size, as in one of our cases, can precede a TCa (35). Occasionally, trauma to the scrotum may reveal the presence of a testicular mass (20). Patients may experience sensations of testicular heaviness or aching or may develop a reactive hydrocele. Rarely, pain is a presenting symptom (36). In about 10% of cases, TCa can mimic an orchioepididymitis, as five of our patients, with consequent delay of the correct diagnosis (36). Thus, any painless lump on a testicle that does not respond promptly to antibiotic treatment must be considered as a TCa. Occasionally, patient presents with signs or symptoms of metastatic disease, including back pain and hydroureteronephrosis (37). Oestrogen-producing tumours can cause loss of sexual desire or gynecomastia which is more common in non-seminomatous tumours. Moreover, diagnosis may be done during the review of infertility data, from clinical examination or ultrasound.

Currently, diagnostic ultrasound serves to confirm the presence of a testicular tumour and to explore the contralateral testis (38). Magnetic Resonance Imaging offers higher sensitivity and specificity than ultrasound for diagnosing tumours (39-42), but its high cost does not justify its use for routine diagnosis. Furthermore, radiological examination will clarify the possible locations of the secondary cancer whether its extension through the lymphatic interesting primarily the para-aortic retroperitoneal lymph nodes or visceral metastasis. The CTScan thoraco-abdomino-pelvic will clarify the seat and the size of these metastases (10). At the end of this exploration and after pathology confirmation, the tumor is classified according to the TNM classification 2002 (5).

Serum tumour markers are prognostic factors and contribute to diagnosis and staging (43). Three markers should be determined: αFP (produced by yolk sac cells), ,-hCG (expression of trophoblasts) and LDH (marker of tissue destruction). Globally, there is an increase in these markers in 51% of cases of TCa (34, 37, 44). It should be noted that negative markers levels do not exclude the diagnosis of a germ cell tumour. Other markers as neuro-specific enolase or placental alkaline phosphatase and cytogenetic and molecular markers are available in specific centers, but at present only contribute to research studies.

Despite all these developments, the diagnosis of TCa always seems that late. The average time between first symptoms and treatment is about 5 months on average (45). It was much longer in our series. One possible explanation is that some regions possess suboptimal health care systems, leading to delay in diagnosis (46). Moreover, patients often trivialize symptoms. Because most cases of TCa do not initially involve pain, for most of our patients, the importance of a testicular nodule may not be considered so important. Huyghe et al demonstrated that diagnostic delay is correlated with more advanced disease stage at the time of diagnosis and reduced significantly the 5-yr survival (47).

Every patient with a suspected TCa must undergo inguinal exploration with exteriorization of the testis within its tunics, and immediate orchiectomy with division of the spermatic cord at the internal inguinal ring (48). This is an orchiectomy with diagnostic and therapeutic objectives (10), frozen section has no place (48). The preservation of semen is routinely offered to the patient but is usually done after orchiectomy if further treatment is indicated (10, 48). In synchronous bilateral TCas, metachronous contralateral tumors or in a TCa in a solitary testis, organ preserving surgery can be performed when the tumor measures less than 2 cm. The option has to be carefully discussed with the patient and surgery performed in a center with experience (49, 50).

TCas arise from germ cells in 94-97% of cases (36, 51). They are classified into seminoma (55 %)(classic, anaplastic and spermatocytic variants) and non-seminomatous germ cell tumours (45 %)(embryonal carcinoma, teratocarcinoma, teratoma, choriocarcinoma, and yolk sac tumours). Non-germ cell tumours include gonadal stromal tumours and miscellaneous neoplasms (51). There is large variations in the distribution of these components within the TCa and different distribution of histological types according to age. Peak incidence is in the 3rd decade of life for non-seminoma and in the 4th for pure seminoma (52). As in our series, African Americans have roughly the same rates of seminoma and nonseminoma as White and Hispanic men (53, 54) but have a lower proportion of embryonic cell carcinoma (12).

The treatment of TCas has greatly evolved from extirpative surgery only, to cisplatin-based chemotherapy, radiotherapy and retroperitoneal lymph node dissection (51).The subsequent depends on the pathology, stage of the tumor, the initial values of serum markers and their changes after orchidectomy, and the existence of risk factors for recurrence (10, 48). The revaluation based on CT Scan after chemotherapy may propose a residual mass surgery (10) as in two of our patients.

All these therapeutic options have made TCa being curable with excellent cure rates and low mortality (55). However, several important factors affect the outcome, including histologic type, careful staging at the time of diagnosis, the mean time delay to diagnosis or to treatment, appropriate early treatment, very strict follow-up and eventual salvage therapies (12, 37). It was reported that survival after a diagnosis of TCa is significantly worse for African Americans than for whites (12), but, we didn't verify these data. The possible reasons for these observed discrepancies include inherent differences in cancer biologic

behavior, healthcare access, socioeconomic factors and differences in baseline co-morbidities (12).

The present study had several limitations. First, it is a single-center study. Second, detailed data regarding CT Scan were only available for 24 patients (about the half). Thus, many of our patients might have been understaged. Third, data are limited regarding the details of the treatment strategies administered to some patients and the important number of "lost to follow-up". Finally, the small numbers of patients lead to questions regarding the generalizability of our results and the precision of the observed outcome data.

We suggest further studies in other Tunisian and Maghrebian hospitals and cancer registries to examine this low and stable incidence in TCa and the trend in histopathologic variant of TCas as highlighted in this study. The confirmation of this low incidence by other investigators may open a new view of research into new ways of decreasing the incidence in other countries and may result in a global reduction of this disease. This is of particular social and economic importance since all variants of TCas have their highest incidence in young adults.

CONCLUSION

The incidence of TCa in Tunisia is low and stable over the two last decades. The reasons for this are unknown. The management of testicular germ cell tumors has greatly benefited from the contribution of chemotherapy and radiotherapy significantly improved the prognosis. The management of testicular cancer in our environment includes challenges such as late presentation, high-stage disease at presentation, and the large number of "lost to follow-up" and "failed to receive adjuvant treatment".

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