Obstructive uropathy in testicular cancer: clinical characteristics at the time of oncologic diagnosis


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KEYWORDS
Obstructive uropathy; Testicular cancer

Abstract

Background: During testicular cancer progression, retroperitoneal activity can condition urinary compression, especially in advanced stages. When this presents, it requires urinary diversion.

Aim: To describe the clinical presentation of obstructive uropathy (OU) associated with testicular cancer at the time of diagnosis, correlating the variables of the neoplasia to establish associations between the 2 entities.

Material and methods: A retrospective study encompassing the time frame from July 2010 to June 2015 was conducted that included 98 patients with testicular cancer, evaluating the presence of OU through abdominal tomography and statistical analysis for the purpose of establishing significant associations between the variables.

Results: Twenty patients (20.2%) presented with OU, with a mean age of 24 years, ECOG 1, and a progression time of 305 days. Eight patients had seminomatous tumor (40%) and 12 had nonseminomatous tumor (60%), of which the most frequent histology was endodermal sinuses (66%), followed by embryonal carcinoma and teratoma (50%, respectively). The mean size of the lymph node conglomerate was 4.3 cm, 65% of the patients had metastasis upon diagnosis, and the most frequent clinical stage was iiiC (50%). Forty percent of the patients had elevated creatinine. There were no statistically significant results between the development of retroperitoneal disease and histology ($P = 0.72$), progression time ($P = 0.44$), or laterality ($P = 0.44$). Testicular tumor size was correlated with the development of OU ($P < 0.05$), the same as stage pT ($P < 0.05$), stage N ($P < 0.05$), metastases ($P = 0.001$), LDH ($P < 0.05$), clinical stage ($P < 0.05$), and young age ($P < 0.05$).

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Conclusions: OU is a comorbidity associated with germ cell testicular cancer that usually involves advanced stages. Young patients with poor functional status, with large tumors, and elevated LDH levels after orchiectomy should be evaluated to rule out urinary compression.

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Introduction

The advances in the treatment of testicular cancer have radically changed in the last 50 years. Before, the possibility of death from the disease once it became metastatic was 90% in the first year, whereas today 95% of the cases of nonmetastatic testicular cancer cases and more than 80% of the metastatic cases are cured.1 During the natural progression of testicular cancer, tumor activity in the retroperitoneum that conditions urinary compression is a relatively frequent cause of morbidity, especially in advanced stages of the disease.2

Urinary flow obstruction can occur at any part of the tract. Obstructive uropathy (OU) can be partial or complete, unilateral or bilateral, acute or chronic, and intrinsic or extrinsic to the urinary tract. Its opportune recognition is essential because it is reversible if rapidly corrected. If not treated opportunely, OU predisposes to conditions ranging from a urinary tract infection to urosepsis and eventually to chronic end-stage kidney disease.3

Aim

To describe the clinical presentation of OU associated with testicular cancer and its relation to specific variables of the neoplasia for the purpose of establishing a possible association between the two eminently urologic entities.

Methods

A retrospective analysis was conducted that included the medical records of 126 patients with preoperative diagnosis of testicular cancer established through the anamnesis, physical examination, preoperative tumor marker tests, and testicular ultrasound.2 The patients underwent open inguinal radical orchiectomy (RO) within the time frame of July 3, 2010 to June 19, 2015 at the Hospital General “Dr. Manuel Gea González”. Once the testicular cancer diagnosis was made, computerized axial tomography (CAT) scan was carried out, either prior to the RO in cases highly suggestive of malignancy or within the first 3 postoperative weeks in
order to establish the clinical stage of the disease and to study the presence of retroperitoneal adenopathies and their possible association with OU. Patients with a histopathologic diagnosis of primary germ cell testicular tumor that had a tomography scan taken within the study period were included. Excluded from the study were those patients that had secondary testicular tumor or non-germ cell etiology, noncancerous testicular masses, patients that did not have a CAT scan within the first 3 postoperative weeks, or that presented with OU not associated with retroperitoneal tumor activity (liathiasis, ureteral stricture, etc.). The SPSS (version 22.0, IBM) software was employed for the statistical analysis. The groups with and without OU were compared, along with their particular clinical and paraclinical variables. The Student’s t test, chi-square test, or Mann-Whitney U test were used to analyze the quantitative or qualitative variables, accordingly.

Results

A total of 126 patients were treated with RO, 117 of whom had primary germ cell testicular tumor. The remaining 9 patients were made up of: 4 patients with clotting or infectious necrosis, 3 with non-Hodgkin’s lymphoma, one patient with Sertoli-Leydig tumor, and one patient with paratesticular liposarcoma, all of whom were excluded from the analysis.

Of the 117 patients with primary germ cell tumor, 19 were excluded because they did not meet the inclusion criteria, whether for loss of follow-up, or lack of CAT for evaluating OU within the first 3 postoperative weeks, or multifactorial loss of clinical information making those cases unreliable or not able to be evaluated.

The 98 remaining patients that met the inclusion criteria were divided into 2 groups: patients with OU secondary to retroperitoneal tumor activity from germ cell testicular cancer and patients with no retroperitoneal tumor activity. The clinical variables of age, height, functional status (evaluated through the Eastern Cooperative Oncology group [ECOG] system, also known as the Zubrod or WHO scale), laterality of the primary tumor (left, right, bilateral), and progression time from symptomatology onset to the time of RO were analyzed in the two groups. Likewise the paraclinical variables: creatinine level, preoperative and postoperative tumor markers, chest and abdominal CAT (contrasted when the serum creatinine and urea levels permitted it), and histopathology report (tumor size, presence of lymphovascular invasion). All the patients were classified according to the TNM system for testicular cancer and clinical stage and prognostic group were assigned (table 1).

Twenty patients presented with OU, representing 20.4% of the cases and 78 patients did not have OU (79.5%). The different variables were compared in the two groups.

Height

A possible association has been pointed out between anthropometric parameters such as height and the risk for testicular cancer. Some case series have reported a very tall height as an increased risk factor for germ cell tumors of the testis, whereas short height appears to be a protective factor. The mean height of our patients was 1.69 m, with a range of 1.50-1.90 m. No statistically significant difference in the mean heights of the patients in the two groups was detected comparing this indicator with the occurrence of OU: (without OU: 1.69 m, with OU 1.70 m) ($t = -0.434$, df = 27.448, $p > 0.05$).

Age

The mean age of the patients was 27.5 years with a range of 14 to 73 years. Comparing the mean age according to OU occurrence, there was a statistically significant difference in the two groups, that is to say, the mean age in the OU group was lower (mean 24.05 years) than in the group without OU (28.41 years), and the range in the first group was 19 to 36 years, different from the range of the group that did not present with OU that was 14 to 73 years (t = 2.901, df = 83.062, $p < 0.05$).

Disease progression from the time of diagnosis

Disease progression time was measured from the onset of symptoms to the time of diagnosis and the mean time in our patients was 6.8 months. Maximum progression time from the time of diagnosis was 61 months: even when a greater maximum progression time was observed in the OU group (61 months compared with 49 in the non-OU group), when the groups were compared, the largest number of patients had a progression time up to diagnosis from 1-12 months, being higher in those that developed OU. Despite that fact, no statistically significant difference was found between the two groups, meaning that behavior in relation to progression time was similar in the two groups ($X^2 = 0.591$, df = 1, $p > 0.01$).

Functional status of the patient

The patients were evaluated at the time of their presentation through the ECOG, described by Oken et al. in 1982. It measures the progression of the daily life capacities of the oncologic patient on a scale from 0 to 5. Our patients had ECOG scores between 0 and 3, none of them reached 4 on the scale and the majority was situated at 0. However, the patients with OU had higher average scores (66.20%).

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Obstructive uropathy n=20</th>
<th>Without obstructive uropathy n=78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Progression time, days</td>
<td>305</td>
<td>140</td>
</tr>
<tr>
<td>Seminoma</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Nonseminoma</td>
<td>12</td>
<td>44</td>
</tr>
<tr>
<td>Postoperative LDH, U/l</td>
<td>1,044</td>
<td>371</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>8.4 × 6.3</td>
<td>5.9 × 4.7</td>
</tr>
<tr>
<td>Retroperitoneal activity</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>Metastasis</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

- **Table 1**: Patient characteristics.
compared with those that did not have OU (42.45%), resulting in a statistically significant difference in the scores of the OU patients (0-3) compared with the scores of the non-OU patients (0-2). (Mann Whitney U: Z = -4.671, p < 0.05)(fig. 1).

Histopathology report

Classically, germ cell testicular cancer is classified as seminoma and nonseminoma and said variable was associated with the presence or not of OU. Of the total (n = 20), 58% were nonseminoma; comparing the histologic type of those patients with and without OU (table 2), the figures for both types are similar with no statistical significance in the two patient groups (X² = .035, df = 1, p > 0.05).

Of the 78 patients without OU, 33 had seminomas (42%) and 45 had nonseminomas (57%), and in the latter the most frequent component was embryonal carcinoma in 36%, followed by teratoma in 34%, and endodermal sinuses in 30% of the cases.

Laterality

The affected side in the greater number of cases was the right side, in more than half (54%). The same behavior was observed in the groups with and without OU and there was no statistical difference between them (X² = 0.413, df = 2, p > 0.05). Therefore, there was no association between the affected side and the possibility of developing OU. Only one patient of the OU group had previous tumor in the contralateral testis, whereas 2 patients in the non-OU group had bilateral metachronous tumor.

Preoperative tumor markers

Alpha-fetoprotein

Alpha-fetoprotein is a glycoprotein produced in the liver that increases under non-malignant conditions such as pregnancy, viral hepatitis, and cirrhosis. In the case of testicular cancer, alpha-fetoprotein is elevated in up to 70% of the patients.7-8

The alpha-fetoprotein values before and after RO were higher in the former, but these differences were not statistically significant as an OU predictor (t= 0.200, df = 81, p > 0.05)

Lactate dehydrogenase

The value of lactate dehydrogenase (LDH) has been related to tumor burden. It is usually stratified as an S value (serum marker) that ranges from S0 to S3 in regard to the postoperative result. In general terms, the largest number of patients was situated in S0 (75%), followed by S2 in 18.8% of the patients. In the LDH comparison in each group (with and without OU), the two groups had patients in the 4 levels (S0 to S3). However, in the non-OU group, the largest number were at the S0 level, unlike the OU group, in which the largest number of patients were at the S2 level (60%), followed by the S0 level with 26% of the patients. The differences were analyzed using the Mann-Whitney U test, and with a 95% confidence level, it produced a statistically significant difference between the distribution of the number of patients with different postoperative LDH levels in the two groups (Z = -5.425, p < 0.05)

Tumor size

Given the difficulties implicit in quantifying tumor size in 3 dimensions, it was decided to estimate the tumor surface based on the dimensions of the tumor measured by the pathologist at the time of slicing the specimen. The tumors measured a mean 34.9 cm², and ranged from 1 cm² to 170 cm², although half of them were over 23 cm².

The parameter analysis of each group showed that the largest tumors corresponded to the OU patients: the mean tumor size in these patients was more than double the size of the tumors in the non-OU group (61.9 cm² vs. 27.8 cm²). In the OU group, half of the tumors measured 51.5 cm² or more and the largest was 154 cm². In the non-OU group, half the tumors measured 16 cm² or less and the largest was 170 cm². In other words, larger tumor size was associated with the development of OU.

<table>
<thead>
<tr>
<th>Pathology report</th>
<th>Without obstructive uropathy (%)</th>
<th>With obstructive uropathy (%)</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>42.3</td>
<td>40</td>
<td>41.8</td>
</tr>
<tr>
<td>Nonseminoma</td>
<td>57.7</td>
<td>60</td>
<td>58.2</td>
</tr>
</tbody>
</table>
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These differences were statistically significant according to the Student’s t test (t = -2.820, df = 20.210, p < 0.05) (fig. 2).

**Grade of testicular invasion (pT)**

Tumor invasion inside and outside the testis is given a grade from 1 to 4 in accordance with the TNM system. In general, in the group of patients studied, the largest number of patients had T2 invasion (56.7%), followed by T1 in 32%. In the analysis by group, the patients with OU had higher invasion grades (T2 and T3) than those without OU (T1 and T2). The differences were evaluated with the Mann-Whitney U test, and with a 95% confidence interval, there was a statistically significant difference in the invasion grades between the two groups. The highest grades were registered in the patients that developed OU (Z = -4.580, p < 0.05)

**Retroperitoneal tumor activity (N)**

With the exception of choriocarcinoma, the lymph canals are the most common dissemination route of the disease from the primary tumor to the retroperitoneal lymph nodes and from there to other sites. The retroperitoneum is the initial metastasis site in 70-80% of the patients with germ cell tumors. In tumors of the right testis, the drains are the infrarenal interaortocaval lymph nodes, followed by the paracaval nodes, whereas for the left side, the primary zone is that of the para-aortic lymph nodes followed by the interaortocaval nodes. Lymph node size was categorized according to the lymph node invasion classification system (N) in testicular cancer that ranges from 0 to 3. In general terms, 4 out of every 10 patients presented with N0 and 4 out of every 10 were > N2.

Upon comparing this indicator according to OU development, more than half did not present with OU (N0), unlike those that developed OU, in which 6 out of every 10 had N3 lymph nodes (larger than 5 cm). These data were analyzed through the Mann-Whitney U test that determined, with a 95% confidence interval, that there was a statistically significant difference between the two groups due to the size of the lymph nodes of the group that developed OU (Z = -5.597, p < 0.05) (fig. 3).

**Metastasis (M)**

Metastatic activity is relatively frequent and is aggressive and lethal if not treated opportune. Metastases presented in 24% of the patients studied. The highest metastasis percentage (65%) was in the OU group. In the non-OU group, only 14.1% of the patients presented with it. These results were compared using the chi-square test and a statistically significant difference was found due to the figure being a bit more than 4 times higher in the OU group than in the non-OU group (X² = 22.300, df = 1, p < 0.05, 95%CI).

The most common metastatic site for the OU group was the lung, followed by the liver, central nervous system, cervical lymph nodes, and mediastinum. One patient presented with atypical metastases to the kidney and celiac plexus, whereas in the non-OU group the lung and liver were the most common sites.

**Creatinine at the time of diagnosis**

Eight percent of the patients had elevated serum creatinine and urea levels, with creatinine > 1.1. The mean creatinine value in the study patients was 0.93, with a range of 0.54 to 2.46. When the groups are compared, the highest values are found in the OU group, but the differences were not statistically significant (t = -0.55, df = 96, p > 0.05), showing that creatinine does not predict OU in testicular cancer.

**Obstructive uropathy location**

In more than half of the patients with OU, obstruction was located on the left side and it was bilateral in only one-fourth of the cases (fig. 4).

**Discussion**

Extrinsic obstruction of the upper urinary tract associated with neoplasia is a relatively frequent phenomenon in oncologic centers. Among the tumors that most frequently condition this pathology are: cervical cancer, colorectal cancer, prostate cancer, bladder cancer, lymphomas, and testicular cancer. They compress the urinary tract when the masses are located in the retroperitoneum or pelvis.
Testicular cancer causes OU due to its infiltration into the retroperitoneal lymph nodes. They become enlarged and extrinsically compress the urinary tract.\(^{16}\) (fig. 5 A and B). The recommended tests in the diagnostic approach include: serum creatinine, ureic nitrogen, and serum electrolytes, along with the imaging studies of kidney ultrasound and tomography.\(^{17}\)

Management options include:\(^{18-19}\)

1. Expectant management: Patients with poor prognosis, those that are asymptomatic with normal kidney function, especially if no other treatment is planned. It is not recommended in symptomatic patients.
2. Endoscopic placement of a ureteral stent: It is first-line management and the stent can be placed in an antegrade or retrograde manner.
3. Percutaneous nephrostomy: It is recommended when it is not possible to place a ureteral stent. It demands more care and precaution and possible complications are also greater.

When retroperitoneal activity and urinary compression are very intense, the patient may require palliative or exclusion nephrectomy.\(^{20}\)

According to our results, it is possible to suspect the presence of urinary compression in patients with testicular cancer at the time of diagnosis. Young age, a deteriorated functional status, bulky tumor size, and elevated LDH levels had a statistically significant correlation with the possibility of urinary compression, which should lead the clinician to suspect lymph node metastasis that involves the urinary tract, requiring a more extensive evaluation at the time of diagnosis.

Older patients, with good functional status, and smaller testicular tumors may have no urinary tract involvement and therefore their evaluation with imaging techniques can be of secondary importance. An exception is choriocarcinoma, because its biologic behavior tends to produce early metastases by way of the bloodstream and to extranodal tissues (nervous system, skin).\(^{21}\)

Likewise, paraclinical tests, such as tumor markers, are recommended preoperatively and postoperatively with special interest in LDH, which suggests intense tumor activity.\(^{22}\)

Despite the fact that variables such as the histopathology report, tumor laterality, preoperative tumor markers, and creatinine were not statistically significant for the development of OU, they enable the prediction of disease behavior and sometimes help regulate therapeutic conduct. Although it is not clear whether height is a risk for testicular germ cell cancer, in our case series it was not a relevant risk factor for OU development.

Even though patients with OU had greater progression times than the patients without OU, and some of them presented with a worse functional status and larger tumors, progression time did not have a statistical correlation with OU development, at least not directly. Even so, the patients with testicular tumors of long progression could present with other types of complications.

There does not seem to be a clear association between the development of obstructive uropathy and histology, in particular, although nonseminomatous germ cell tumors

**Figure 4** Obstructive uropathy location

**Figure 5** A) Left ureteral compression due to retroperitoneal tumor activity. B) Retroperitoneal mass bilaterally compressing the collecting system with predominance on the right side and requiring ureteral diversion.
appear to present more frequently, especially when there is an embryonal carcinoma, teratoma, or yolk-sac tumor component. Right testicular tumors were more frequent than tumors of the left testis in our case series, which was not a determining factor for the development of OU.

Conclusions

OU should be suspected in patients with advanced stage testicular cancer, considering it a negative factor that deteriorates quality of life and that can require treatment. OU can be found with relative frequency in germ cell testicular cancer and it was identified in 20% of our population at the time of diagnosis.

OU should be suspected in young patients, when there is poor functional status, in large tumors, and when there are high LDH levels, and an imaging study should be carried out for early corroboration.

A larger number of patients are needed to be able to perform a more accurate logistic regression analysis and determine the definitive impact that these eminently urologic entities have on each other. Prospective studies are required that evaluate the impact that OU appears to have on disease outcome.

Ethical responsibilities

Protection of persons and animals. The authors declare that no experiments were performed on humans or animals for this study.

Data confidentiality. The authors declare that they have followed the protocols of their work center in relation to the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Financial disclosure

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Conflict of interest

The authors declare that there is no conflict of interest.

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Reference