Do retroperitoneal extragonadal germ cell tumours exist?

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Cite as: Can Urol Assoc J 2015;9(11-12):381-4. http://dx.doi.org/10.5489/cuaj.3024 Published online December 14, 2015.

Abstract

Introduction: Extragonadal germ cell tumours (GCTs) have been described arising in midline structures. Although primary retroperitoneal extragonadal GCTs (RPGCTs) comprise 30% to 40% of these, their existence as a genuine disease has been questioned. Our study evaluated clinicopathological findings to examine this question in RPGCT patients at our centre.

Methods: Data from 414 men between 1980 and 2014 treated at London Health Sciences Centre with chemotherapy for testicular GCTs were reviewed retrospectively. Primary RPGCT was defined as pathologically diagnosed GCT with no evidence of GCT in the testes by physical exam or ultrasound. Patients thought to have primary RPGCT at the time of initial diagnosis were identified from an electronic database and data were extracted.

Results: In total, 18 men with a diagnosis of metastatic RPGCT were identified. Four were excluded due to ultrasound reports that were incomplete or suggested malignancy. The remaining 14 patients had negative or non-specific ultrasounds, and all received platinum-based combination chemotherapy. Ten patients (71%) underwent post-chemotherapy RP lymph node dissections; of those 8 (57%) who underwent orchietomy, none had corresponding pathologically normal testicular tissue.

Conclusion: RPGCT patients present with more advanced disease stage. Our study sample size is limited, but the findings are consistent with existing literature suggesting that primary RPGCTs may not exist as a unique disease, but instead may represent metastatic disease from a clinically occult testicular primary. By corollary, viable malignant germ cells may be present in testes of patients with presumed primary RPGCT, and may persist as a site of residual malignant disease after chemotherapy.

Introduction

Extragonadal germ cell tumours (GCTs) are uncommon and typically arise from the pineal gland, mediastinum, sacrococcyx, or retroperitoneum, and rarely in the vagina, prostate, liver, gastrointestinal tract and orbits.1-3 Primary retroperitoneal extragonadal GCTs (RPGCTs) account for 30% to 40% of extragonadal GCTs.4 The only cohort study investigating RPGCTs suggests that these may not represent a distinct clinical entity, but rather metastases from a clinically occult primary testicular tumour.1,5

Some studies have suggested that RPGCTs and primary testicular tumours with retroperitoneal metastases are 2 entirely different diseases.6 However, treatment of presumed RPGCT is identical to that of testicular GCT, with the exception of the use of orchidectomy.4,7 If there remains uncertainty about the origin of RPGCTs and doubt regarding residual disease in the testicle, missed disease might remain in the testicle and serve as a source for recurrence and metastases.5

Based on the uncertainty and limited evidence available in the literature, we reviewed all presumed RPGCTs at our centre to investigate the evidence supporting RPGCT as a unique diagnostic entity. A clear understanding of this concept is important to optimize management and testicular preservation.

Methods

Men treated at London Health Sciences Centre between 1980 and 2014 for metastatic GCTs were identified from an electronic database and screened for a diagnosis of RPGCT. The site of origin for the primary tumour was recorded for all patients in the database, and patients with retroperitoneal primary tumour were identified with an electronic filter. To be eligible, patients had to have pathologically diagnosed GCT with metastatic disease and no evidence of tumour in the testes by physical exam or on ultrasonography. Patients were excluded if there was incomplete data or if their treat-
Physician did not give them a diagnosis of RPGCT.

Demographic and clinical data, including IGCCCG (International Germ Cell Classification Collaborative Group) classification, treatment details, and clinical outcomes, were extracted from the database and original medical records as necessary. Individual pathology from orchiectomy and retroperitoneal lymph node dissection procedures were recorded. Orchiectomies were completed in patients with negative ultrasound findings at the discretion of the surgeon for concern of the remaining testicles acting as a sanctuary for disease. The orchiectomy side was chosen based on the presumed primary landing zone. Additionally, ultrasound findings completed upon initial workup were recorded. Results that were reported as non-specific reflect no concerning findings for malignancy.

Descriptive statistics were used to analyze the data. This study was approved by the Western University Research Ethics Board.

Results

Of the 414 men treated between 1980 and 2014 for metastatic GCTs, 18 with RPGCTs were identified. Four of these were excluded due to incomplete imaging reports or reports suggestive of malignancy. The 14 remaining included patients were considered to have RPGCT at the time of initial diagnosis (Fig. 1).

We tallied patient demographics and baseline characteristics (Table 1). The median age was 33 (range: 24–45). Pre-chemotherapeutic tumour markers were elevated in about half of included patients, and serum lactate dehydrogenase was elevated in almost all included patients. IGCCCG prognostic stages were as follows: good in 3 patients (21%); intermediate in 6 patients (43%); and poor in 5 patients (36%). Four of the poor prognosis patients were classified as such due to elevated tumour markers, 3 received BEP (bleomycin, etoposide, cisplatin) chemotherapy, and only 1 in 5 patients had salvage therapy. Overall, all patients received systemic cisplatin-based chemotherapy, with most receiving BEP (71%).

We tallied the clinical details of all 14 patients (Table 2). Eight patients had orchiectomy and pathology described viable malignancy in 3 patients (21%), and testicular fibrosis or scarring following chemotherapy in 5 patients (35%). Of the 14 patients, 10 had post-chemotherapy retroperitoneal lymph node dissection (RPLND), and corresponding testicular pathology was available in 8 of these cases. None of these 8 patients had corresponding normal testicular pathology in the context of abnormal RPLND pathology. In the 2 cases without corresponding testicular pathology, the RPLND pathology was consistent with scarring or fibrosis secondary to chemotherapy. Overall survival data were incomplete due to patients lost to follow-up.

Discussion

Extragonadal GCTs remain controversial with respect to their origin, natural history, and treatment. The existence of primary RPGCTs, which account for about one-third of these tumours, has been previously questioned. The accepted theory is that these tumours originate from displaced germ cells during embryonic development in the fetus.
Patients with primary RPGCT had more advanced disease stage. Less than one-quarter of the patients in our study presented with IGCCCG good prognosis disease, whereas typically this is 60% to 70% in most series.9 Most patients presented with intermediate or poor prognosis IGCCCG disease, and the incidence of the latter was doubled. This should not be surprising with the lack of an enlarging testicular mass to serve as a clinical “trigger” for the patient seeking medical attention.

Our study was unable to identify patients with abnormal pathology in their retroperitoneal mass and corresponding normal testicular pathology. Many of these patients had testicular fibrosis and scarring suggestive of “burnt-out” malignant disease, suggesting primary tumour regression.10-12 This supports the assertion that primary retroperitoneal GCTs may not exist as a distinct disease entity, but rather that this clinicopathological syndrome may be representative of metastatic disease originating from a clinically occult testicular primary.1,5

This distinction has clinical importance in the management of the testes in men with the metastatic RPGCT syndrome. If correct, there should be concern about the presence of viable germ cell malignancy in the testes of these patients, which could serve as a potential source for recurrence.10 More rigorous evaluation using physical exam, radiographic imaging and laboratory investigations must be completed to further elucidate any trends or characteristics to help further guide management.1,5 For example, subtle ultrasonographic findings that are often considered negative may represent disease.2,5 Some studies have questioned the role of testicular biopsy and suggest that it is not routinely justified.2 Routine management with orchiectomy would overtreat patients without viable GCT.10 So the optimal approach remains unclear.

The conclusions of our study are limited by its small sample size. We identified patients over a long time period at a tertiary academic centre and the incidence of primary RPGCT was relatively low. Our study was retrospective, and variability would be increased by multiple physicians completing pathologic and radiographic reports over the time period reviewed due to the inherent subjectivity in the initial diagnosis of a RPGCT. We could not comment on the role of physical examination of the testes based on limited data reporting, but this is considered a standard procedure in the investigation of a GCT.5

**Conclusion**

Although an uncommon presentation at our centre, further information from large multicentre databases could provide enhanced information about patients presenting with a primary retroperitoneal GCT to optimize management.

**Competing interests:** Dr. Punjani declares no competing financial or personal interests. Dr. Winquist is currently participating in clinical trials with AstraZeneca, Exelixis, Janssen, Roche, and Medivation. Dr. Power is currently participating in clinical trials with Arqos Therapeutics.

**References**


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**Table 2. Individual patient clinical data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Chemotherapy</th>
<th>Ultrasound findings</th>
<th>Orchiectomy</th>
<th>Testicular pathology</th>
<th>RPLND</th>
<th>Final RPLND pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BEP</td>
<td>Negative for malignancy</td>
<td>Yes</td>
<td>Post-chemotherapy Scar</td>
<td>Yes</td>
<td>Necrosis</td>
</tr>
<tr>
<td>2</td>
<td>PVB/PE</td>
<td>Negative for malignancy</td>
<td>No</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>BEP</td>
<td>Non-specific</td>
<td>Yes</td>
<td>Seminoma</td>
<td>Yes</td>
<td>Necrosis</td>
</tr>
<tr>
<td>4</td>
<td>PVB</td>
<td>Negative for malignancy</td>
<td>No</td>
<td>N/A</td>
<td>Yes</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>5</td>
<td>BEP</td>
<td>Non-specific</td>
<td>Yes</td>
<td>Embryonal carcinoma</td>
<td>Yes</td>
<td>Viable GCT (embryonal, teratoma, seminoma)</td>
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<tr>
<td>6</td>
<td>VIP</td>
<td>Non-specific</td>
<td>No</td>
<td>N/A</td>
<td>Yes</td>
<td>Necrosis</td>
</tr>
<tr>
<td>7</td>
<td>BEP</td>
<td>Negative for malignancy</td>
<td>No</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>PIE</td>
<td>Non-specific</td>
<td>Yes</td>
<td>Post-chemotherapy scar</td>
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<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>9</td>
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<td>Negative for malignancy</td>
<td>Yes</td>
<td>Post-chemotherapy scar</td>
<td>Yes</td>
<td>Metastatic seminoma</td>
</tr>
<tr>
<td>10</td>
<td>BEP</td>
<td>Negative for malignancy</td>
<td>Yes</td>
<td>Post-chemotherapy scar</td>
<td>Yes</td>
<td>Fibrosis and necrosis</td>
</tr>
<tr>
<td>11</td>
<td>BEP</td>
<td>Non-specific</td>
<td>Yes</td>
<td>Post-chemotherapy scar</td>
<td>Yes</td>
<td>&lt;5% mature teratoma</td>
</tr>
<tr>
<td>12</td>
<td>BEP</td>
<td>Non-specific</td>
<td>No</td>
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<td>N/A</td>
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<td>13</td>
<td>BEP</td>
<td>Negative for malignancy</td>
<td>Yes</td>
<td>Rare intratubular germ cell neoplasia</td>
<td>Yes</td>
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</tr>
<tr>
<td>14</td>
<td>BEP</td>
<td>Negative for malignancy</td>
<td>No</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
</tr>
</tbody>
</table>

RPLND: retroperitoneal lymph node dissection; BEP: bleomycin, etoposide, cisplatin; PVB: cisplatin, vinblastine, and bleomycin; PE: cisplatin, etoposide; PIE: cisplatin, ifosfamide, and oral etoposide; N/A: not available; GCT: germ cell tumour.


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