Germ cell tumor: A seven-year experience
Children Welfare Teaching Hospital

Abstract:

**Background:** Germ cell tumors are a rare heterogeneous group of cancers with high cure rates in the pediatric age group.

**Objectives:** To study the clinical and pathological features in a group of patients with germ cell tumors and to evaluate their outcomes.

**Patients and methods:** A record review was undertaken on a group of patients with germ cell tumor who were admitted to the Children Welfare Teaching Hospital in Baghdad during the years 2009 - 2015. Information on gender, age, clinical signs, pathological findings, treatment and overall survival rate were reviewed.

**Results:** The patients had a mean age of 4.2 years (ranging from 1 month - 14 years). There were 45 girls and 16 boys. Abdominal pain was the most common presentation in 17 patients followed by a lower back mass in 16 patients. Primary sites included extra gonadal (sacrocccygeal 18, pelvis 5, vagina 4, gluteal 3, intra-cardiac, and one each for the mediastinum, orbit and rectum), and gonadal (18 ovarian and 9 testicular). After a mean period of follow-up of 42 months, the overall survival at 1 year was 59%.

**Conclusion:** The prognosis of children with germ cell tumors is favorable, regardless the site and histopathology.

**Keywords:** Germ Cell Tumor, Children Welfare Teaching Hospital.

Introduction

Germ cell tumors (GCT) are classified as malignant or benign tumors (1). They consist of a wide variety of tumors which originate from primordial germ cells. Although all of them have the same origin, they are different in their pathological behavior and clinical presentation. These types of tumors are not common comprising only 4% of childhood cancer (1). The most common types of GCT are: Teratomas, germinomas, endodermal sinus tumor or yolk sac tumors (YSTs) (2), choriocarcinoma and embryonal carcinoma. Yolk sac tumors are the most prevalent malignant tumors of the gonads in the pediatric age group (1).

Patients and methods

A record review study of 61 patients with the pathological diagnosis of GCT who were treated in the Children Welfare Teaching Hospital over seven years from January 1st, 2009 - December 31st, 2015 were included in the study (last follow up till December 31st, 2016).

Two patients were excluded from the study (they were initially treated as rhabdomyosarcoma, and then changed to germ cell tumor protocol according to telemedicine consultation). Demographic data, clinical signs and symptoms, tumor site, histopathology, biochemical assay, mode of diagnosis, treatment modalities and outcome all were reviewed from the patients' original medical records of inpatient and outpatient clinic files. The diagnosis was based on surgery and histopathology in nearly all cases. In a few cases we relied on fine needle aspiration cytology (FNAC) either because the patient was in a critical condition or the biopsy was not feasible. The histopathological specimens of 37/61 of patients were reviewed and confirmed to be malignant GCT or immature teratoma in department of pathology, La Spienza University, Rome. Risk group stratifications and clinical staging were adopted according to UKCCSG –GCT III protocol for patients diagnosed in 2015. Patients diagnosed in 2009-2014 were retrospectively staged (3). The postoperative adjuvant chemotherapy with four-six cycles of Carboplatin-Etoposide-Bleomycin (JEB)(3) was administered if the histology was reported as malignant GCT or immature teratoma. All other types were treated with the same protocol as recommended globally. For relapsed cases we used VeIP protocol for relapse & refractory cases (6 cycles, 3 weeks apart). Follow-up during treatment based on clinical evaluation, tumor marker (AFP &
HCG) estimation (whenever available or possible) and by imaging studies. Follow up of patients over a period of one year was carried out either in person at the outpatient clinic or by phone call. The overall survival was defined as the time from enrolling in the study until death or last reported contact. (4)

Statistical analysis:
Patients’ data were tabulated and processed using SPSS (Statistical package for the social sciences) V 20 for mac. Data were expressed as frequencies, percentages, and median.(4)

Results:
The mean age of the cases was 4.2 years (ranging from 1 month - 14 years). More than 70% of the patients were less than four years of age at presentation. There was a female predominance where 45 of the cases (73.8%) were females with a male to female ratio 0.35: 1, table 1.

The most common presentation was abdominal pain in 17 (27.9%) patients, followed by lower back swelling in 16 (26.2%) patients, abdominal distention and difficulties in urination in 13 (21.3%) patients each, fever in 12 (19.7%) patients, and pallor in 11(18%) patients. The less common presentations were: Nausea and vomiting, painless testicular swelling, constipation, gluteal mass, abdominal mass, poor oral intake, vaginal bleeding, ribbon like stool, weight loss, cough, dyspnea, rectal prolapse, and proptosis, table 2.

Table 1: Distribution of the cases by age group and gender

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4 Years</td>
<td>43</td>
<td>70.5</td>
</tr>
<tr>
<td>4-10 Years</td>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>&gt; 10 Years</td>
<td>12</td>
<td>19.7</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>26.2</td>
</tr>
<tr>
<td>Female</td>
<td>45</td>
<td>73.8</td>
</tr>
</tbody>
</table>

The most common histopathological subtype was yolk sac tumor in 37 (60.7%) patients, followed by immature cystic teratoma in 20 (32.8%) patients, lastly dysgerminoma and sex cord tumor in 2 (3.3% for each). It was found that in all histopathological types female were predominant, but not significantly so (P-value 0.08), table 4.

The most prevalent stage at the time of diagnosis was stage IV in 20 (32.8%) patients followed by stage II in 18 (29.5%) patients, while in 4 (6.6%) patients the staging was unknown, table 6.
Fifty-nine patients out of 61 received chemotherapy with JEB protocol (carboplatin (JM8), etoposide phosphate, and bleomycin sulfate). Forty-seven patients (80%) completed the treatment, 6 (10%) patients died during treatment, 6 (10%) patients had progressive disease. Out of the 47 treated patients, 33 (70%) were alive, 6 (13%) were alive but relapsed, 4 (8.5%) died and 4 (8.5%) were lost to follow up. From total of 22 deaths, 15 (68%) had yolk sac tumor and the remaining 7 (32%) had immature teratoma, Table 6. Figure 1 shows the overall survival rate of the cases.

Table 6: Distribution of the cases by treatment outcome (59/61 patients)

<table>
<thead>
<tr>
<th>Outcome after finishing treatment</th>
<th>Item</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Completed treatment</td>
<td>47</td>
<td>79.6</td>
</tr>
<tr>
<td>Died</td>
<td>6</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>Progressive</td>
<td>6</td>
<td>10.2</td>
<td></td>
</tr>
</tbody>
</table>

| Time of death in 22 / 59 patients | Died during treatment | 10 | 45.4 |
|                                   | Progressive disease on treatment | 6 | 27.3 |
|                                   | Relapse on treatment           | 6 | 27.3 |

<table>
<thead>
<tr>
<th>Histopathology of 22 dead patients</th>
<th>Yolk sac tumor</th>
<th>15</th>
<th>68.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immature teratoma</td>
<td>7</td>
<td>31.8</td>
</tr>
</tbody>
</table>

Fig. 1: The overall survival rate of the cases
The mean duration of follow up was 42 months
The one year overall survival was 59%

Discussion:
GCTs are a rare and diverse group of heterogeneous tumors that include both benign and malignant histologies (5). The current study showed a female predominance (73.8%) which is in agreement with the study of Fedhila et al in Tunis 2016(6) which showed a female predominance of (58%) and the study of Neyssa Marina et al in Florida – USA 2006 (7) which showed a (66%) female predominance. This can be attributed to the fact that germ cell cancers start in the cells that would form ova in the ovary. All patients were symptomatic at presentation, most commonly with abdominal pain. Fakhr (8) in his study of 34 patients, found that abdominal swelling (18 patients, 52.9%) was the most common initial presentation. In the current study the anatomic distribution of GCTs according to organ involvement was either gonadal in 27 (44.2%) cases or extra-gonadal in 34 (55.8%) cases. Khaleghnejad-Tabari et al (1) found gonadal involvement in (27.27%) of the cases and extra-gonadal involvement in (72.72%) of the cases, while Fakhr et al (8) found gonadal involvement in (61.8%) of the cases and extra-gonadal in (38.2%) of the cases. Fedhila, et al (6) found gonadal involvement in (51.5%) of the cases and extra-gonadal involvement in (48%) of the cases. In the current study, the most common pathologic type was yolk sac tumor in 37 (60.7%) of the cases, whereas Khaleghnejad-Tabari et al (1) found that the most common pathologic type was mature teratoma in (40.9%) of the cases and yolk sac in (31.8%) of the cases. This might be explained by the fact that both malignant and benign GCTs were included in Khaleghnejad-Tabari study. Fakhr et al (8) found that the most common histologic subtypes were yolk sac tumor and malignant teratoma, which were diagnosed in (38.2%) of the cases each. Ansari (9) in a study of 57 patients found that yolk sac tumor was the most common pathology in (61.4%) of the cases. The study showed a higher incidence of yolk sac tumors and malignant teratoma due to the referral of malignant cases only. Death was reported in 22 (37%) patients, 10 of whom died during treatment, 6 died with progressive disease and 6 with a relapse on treatment. Fedhila, et al (6) reported 6 (18.2%) deaths caused by tumor progression in 3 cases, metastatic relapse in spite of second line chemotherapy in 2 cases, and chemotherapy side effects in one case. Khaleghnejad-Tabari (1) reported 9 deaths (22.5%), while Fakhr et al (8) reported two deaths only (6%) due to disease progression. The high death rate in our study reflects the advanced stages at presentation. Out of the 22 cases which died in our series 15 had yolk sac histology (68%) although they constituted (60.7%) of the cases. Khaleghnejad-Tabari (1) reported that 8 of the 13 who died (61.5%) had yolk sac tumor. De Backer et al (10) reported that deaths were higher among those with immature teratoma and mixed GCT. After a mean follow up period of 42 months in the current study, the one-year overall survival rate was 59%. Fakhr et al (8) reported a three-year overall survival of 92% with a mean follow up period of 52 months. Fedhila, et al (6) with a mean follow up period of 26.1 months, reported a two-year overall survival of 82%. Kim et al (11) reported that the five-year overall survival was 92%. These differences might be attributed to differences in the tumor stages and their pathological behavior between these studies.
Conclusions:
The prognosis of children with germ cell tumors is favorable, regardless the site and histopathology. Due to the better survival rates seen in studies different other countries, we need to focus on improving the outcomes of Iraqi children with GCT through collaborative research and multi-center clinical trials. There is a need for the initiation of multidisciplinary groups that have the capability of improving the quality of life of cancer patients.

Authors’ Contributions:
Raghad M. al-Saeed MD & Afrah M. Jassim MD (collecting data)
Samaher A. Razaq MD (review the data)
Mazin F. AL-Jadiry MD (data analysis)

References
ورم الخلايا الجرثومية: تجربة لمدة سبع سنوات

الخلاصة:
خلفية الدراسة: أورام الخلايا الجرثومية هي مجموعة نادرة غير متجانسة من السرطانات مع معدلات علاج عالية في الفئة العمرية للأطفال.
الهدف من الدراسة: دراسة السمات السريرية والمرضية في مجموعة من المرضى الذين يعانون من أورام الخلايا الجرثومية وتقييم نتائجهم.
المرضى وأساليب الدراسة: تم إجراء مراجعة قياسية لمجموعة من المرضى المصابين بورم الخلايا الجرثومية الذين تم إدخالهم إلى المستشفى التعليمي لرعاية الأطفال في بغداد خلال السنوات 2009-2015. وجرى استعراض المعلومات المتعلقة بنوع الجنس والعمر والعلامات السريرية والنتائج المرضية والعلاج ومعدل البقاء العام.
النتائج: كان متوسط عمر المرضى 4.2 سنة (تتراوح بين شهر واحد - 14 سنة). وكان هناك 45 قتآ و16 صبيا. وكان ألم البطن العرض الأكثر شيوعا في 17 مريضا تليه كتلة أسفل الظهر في 16 مريضا. وشملت المواقع الأولية واسعة. وشملت السرطانات الأفقية عند مريضا، وشملت المواقع الأولية واسعة. وشملت السرطانات الأفقية عند مريضا، وشملت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية واسعة. وتميزت المواقع الأولية W
الاستنتاج: التكهنات الخاصة بالأطفال الذين يعانون من أورام الخلايا الجرثومية إيجابية، بغض النظر عن موقع أو التحليل النسيجي لورم الخلايا الجرثومية – مستشفى حماية الأطفال التعليمي.
الكلمات الأساسية: أورام الخلايا الجرثومية– مستشفى حماية الأطفال التعليمي.