Tumors of Bilateral Streak Gonads in Patients with Disorders of Sex Development Containing Y Chromosome Material

Fumi Matsumoto¹, Kenji Shimada¹, and Shinobu Ida²
¹Department of Urology, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan
²Department of Gastroenterology, Nutrition and Endocrinology, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

Abstract. The presence of Y chromosome material in patients with disorders of sex development (DSD) has been associated with a high risk of gonadoblastoma. Therefore, gonadectomy is recommended in females with bilateral streak gonads and Y chromosome material. The aim of this study was to present our experience with prophylactic gonadectomy in those patients and evaluate their risk of gonadal tumors. We reviewed the charts of 11 female patients who had bilateral gonadectomy (by laparoscopically in 9 patients, by laparotomy in 2 patients) between 1991 and 2012 at our hospital. Seven patients with Turner syndrome (TS) who carry a Y mosaic karyotype in peripheral blood, 3 patients with Swyer syndrome and one patient with Frasier syndrome were included. All patients had an unambiguous female phenotype. Age at surgery and follow-up ranged from 2 to 23 (mean 11) and 0.5 to 20 (mean 8) yr, respectively. Pathologic examination revealed gonadal tumors in 6 of 11 patients (56%), including 4 with TS, the youngest of which was 2 yr old, one with Swyer syndrome and one with Frasier syndrome. A gonadoblastoma was detected in 8 gonads, and an association of dysgerminoma with gonadoblastoma was detected in 2 gonads. Imaging studies showed no metastasis, and the postoperative course was uneventful in all patients. In our series of DSD patients with bilateral streak gonads and Y chromosome material, the risk of gonadal tumor was high. Considering the early occurrence of gonadoblastoma and its high potential for malignant transformation, early prophylactic gonadectomy is strongly recommended.

Key words: gonadoblastoma, streak gonad, disorders of sex development, Y chromosome

Introduction

Disorders of sex development (DSD) are defined as congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical (1). The overall occurrence is estimated to be one in 4500 to 5000 live births (1). In specific group of DSD patients, i.e., those bearing Y chromosome material, an increased risk of gonadal tumor
has been reported(1–3). The gonadoblastoma (GB) composed of germ cells and stromal cells, which is the in situ germ cell malignancy of the ovary and dysgenetic gonad, has the potential to progress towards invasive germ cell tumor (GCT) in 60% of the cases, particularly dysgerminoma, and less frequently, towards components of other tumors, such as embryonic carcinoma, teratoma, yolk sac tumor and choriocarcinoma (4, 5). Traditionally, the prevalence of GB and GCT in patients with Y chromosome material is estimated to be larger than 30% (6, 7). However, the reported prevalences may vary due to limited numbers of the patients. In this study, we present our experience with prophylactic gonadectomy in patients with bilateral streak gonads and Y chromosome material and our assessment of the risk of gonadal tumor development.

**Subjects and Methods**

We reviewed the charts of 11 female patients who had bilateral gonadectomy (by laparoscopically in 9 patients, by laparotomy in 2 patients) between 1991 and 2012 at our hospital. All patients were suspected to have bilateral streak gonads by endocrinological examination and imaging studies preoperatively. Seven patients with Turner syndrome (TS) who carry a Y mosaic karyotype, 3 patients with Swyer syndrome and one patient with Frasier syndrome were included. Karyotyping was performed by classical cytogenetic analysis using peripheral blood lymphocytes. No patient with Swyer syndrome had mosaicism (all 3 patients had a 46,XY karyotype) or syndromic features. In a 46,XY patient with Frasier syndrome, analysis of the WT1 gene confirmed a mutation, IVS9+4C>T. All patients had an unambiguous female phenotype. Operative findings showed bilateral streak gonads located in the abdominal cavity in all cases. Age at surgery and follow-up ranged from 2 to 23 (mean 11) and 0.5 to 20 (mean 8) yr, respectively.

**Results**

Pathologic examination revealed gonadal tumors in 6 of 11 patients (56%), including 4 of 7 patients (57%) with TS, one of 3 patients (33%) with Swyer syndrome and the one patient with Frasier syndrome. The youngest patient was a 2-yr-old girl with TS. Four of these 6 patients (67%) had bilateral tumors. A gonadoblastoma was detected in 8 gonads, in 5 patients, and an association of dysgerminoma with gonadoblastoma (Fig.1) was detected in 2 gonads, in 2 patients (Table 1). Imaging studies performed after surgery, including a thoracoabdominal computerized tomography scan, revealed no sign of metastasis in the 2 patients in which an association of dysgerminoma with gonadoblastoma was detected. The postoperative course was uneventful in all of 11 patients.

**Discussion**

The risk of gonadal tumor is an important factor in the management of patients with DSD. DSD patients with Y chromosome material in particular have an increased risk of developing an invasive GCT. The reported prevalence of GB and invasive GCT varies, but it is estimated to
be over 30% in patients with gonadal dysgenesis and is often bilateral (6–8). Therefore, in the consensus statement in 2006 (1), prophylactic gonadectomy was recommended in patients with bilateral streak gonads containing Y chromosome material, because hormonal production and fertility were not expected.

TS is one of the most common chromosomal abnormalities in humans, and is present in 1:2000 newborns with a female phenotype (9). Although TS is characterized by sex chromosome monosomy (45,X), several mosaicism of both the X and Y chromosome is found in up to 50% of patients (9, 10). In routine cytogenetic analysis the Y chromosome or Y-specific sequence is present in about 5% of the patients with TS (9).

Brant et al. (11) reported that GB was detected in 3 of 7 patients (43%) with TS carrying Y mosaicism. No invasive GCT was found in their series of prophylactic gonadectomy, whereas an association of dysgerminoma was detected in a half of our TS patients with GB. It is possible that a difference in screening methods for Y chromosome material may influence the results. Using molecular techniques such as fluorescence in situ hybridization or polymerase chain reaction, the detection of low frequency cell lines and possible structural anomalies is improved (12–14). Some authors reported that polymerase chain reaction is more effective than cytogenetic analysis for detecting hidden Y chromosome material (13, 14). However, Cools et al. (8) reported that the prevalence of GB in patients with TS having hidden Y chromosome material is low (11.6%, 5 out of 43 patients). Therefore, we only performed standard lymphocyte karyotyping.

In 1955, Swyer described two cases of sex reversal that had a 46,XY karyotype and had primary amenorrhea, tall stature, female external genitalia and normal Mullerian structures (15). Patients with Swyer syndrome have bilateral streak gonads and are also known as a member of pure gonadal dysgenesis. A deletion in the DNA-binding region of the SRY gene is found in 10–20% of the affected patients. The incidence of this condition is estimated to be 1:80,000 birth (16). The risk of gonadal tumor (GB and dysgerminoma) in patients with Swyer syndrome has been estimated to be 15–30% (1). In our study GB was detected in one of 3 patients (33%).

Pure gonadal dysgenesis is the consequence of an abortive development of the fetal testis. In some cases the mutations in specific genes, such as SRY, SOX9, SF1, DAX1, WT1, or other unknown genes involved in testis differentiation are reported (17). Frasier syndrome, characterized by gonadal dysgenesis in 46,XY individuals and

---

**Table 1 Characteristics of the patients with bilateral streak gonads**

<table>
<thead>
<tr>
<th>Case</th>
<th>Disorder</th>
<th>Karyotype</th>
<th>Symptom</th>
<th>Age at gonadectomy</th>
<th>Gonadal lesion (Rt)</th>
<th>Gonadal lesion (Lt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Turner</td>
<td>45,X/46,XY</td>
<td>Short stature</td>
<td>9 yr 10 mo</td>
<td>No tumor</td>
<td>No tumor</td>
</tr>
<tr>
<td>2</td>
<td>Turner</td>
<td>45,X/45,X; (p11.2;q11.2)</td>
<td>Short stature</td>
<td>2 yr 11 mo</td>
<td>GB</td>
<td>GB</td>
</tr>
<tr>
<td>3</td>
<td>Turner</td>
<td>45,X/46,XY</td>
<td>Low weight</td>
<td>5 yr 5 mo</td>
<td>No tumor</td>
<td>No tumor</td>
</tr>
<tr>
<td>4</td>
<td>Turner</td>
<td>45,X/46,XY</td>
<td>Short stature</td>
<td>10 yr 3 mo</td>
<td>GB</td>
<td>GB</td>
</tr>
<tr>
<td>5</td>
<td>Turner</td>
<td>45,X/46,XY</td>
<td>Short stature</td>
<td>11 yr 6 mo</td>
<td>GB+dys</td>
<td>No tumor</td>
</tr>
<tr>
<td>6</td>
<td>Turner</td>
<td>46.X,+der(15)/46,XY</td>
<td>Short stature</td>
<td>15 yr 4 mo</td>
<td>GB</td>
<td>GB+dys</td>
</tr>
<tr>
<td>7</td>
<td>Swyer</td>
<td>46,XY</td>
<td>Amenorrhea</td>
<td>17 yr 3 mo</td>
<td>No tumor</td>
<td>No tumor</td>
</tr>
<tr>
<td>8</td>
<td>Swyer</td>
<td>46,XY</td>
<td>Amenorrhea</td>
<td>23 yr 6 mo</td>
<td>No tumor</td>
<td>GB</td>
</tr>
<tr>
<td>9</td>
<td>Turner</td>
<td>45,X/46,XY</td>
<td>Short stature</td>
<td>10 yr 6 mo</td>
<td>No tumor</td>
<td>No tumor</td>
</tr>
<tr>
<td>10</td>
<td>Swyer</td>
<td>46,XY</td>
<td>Short stature</td>
<td>4 yr 5 mo</td>
<td>No tumor</td>
<td>No tumor</td>
</tr>
<tr>
<td>11</td>
<td>Frasier</td>
<td>46,XY</td>
<td>Proteinuria</td>
<td>12 yr 0 mo</td>
<td>GB</td>
<td>GB</td>
</tr>
</tbody>
</table>

GB indicates gonadoblastoma; dys, dysgerminoma.
nephropathy, is caused by mutations in the WT1 gene (18). These mutations occur mainly in the donor splice site within intron 9 and lead to a relative reduction in the production of the +KTS WT1 isoform, which has been shown to be important in gonadal development (19). The incidence of 46,XY Frasier syndrome is unknown because it is difficult to distinguish it from Denys-Drash syndrome, another overlapping disease caused by WT1 gene mutations, is difficult and little data is available (20). Since Frasier et al. (21) reported the first case in 1964, more than 60 cases have been reported (20, 22, 23). The prevalence of GB in patients with Frasier syndrome is very high. Taking into consideration the previous literature, and the as one patient in our series, GB was detected 22 of 45 patients (49%) with Frasier syndrome (23), and the risk of GCT was estimated to be 60% (1). Because of the limitations of chemotherapy in patients with renal insufficiency, early gonadectomy is recomended.

GB commonly occurs in the second decade of life but can develop in children with gonadal dysgenesis as early as age of 9 mo (24). In our study the youngest patient was 2 yr and 11 mo old, and two other patients were diagnosed with GB associated with dysgerminoma as teenagers. Therefore gonadectomy should be considered soon after the diagnosis of streak gonad is made in females with Y chromosome material.

The limitations of this study include its small sample size and the heterogeneous etiology of materials. However, our results may contribute to the better understandings of these very rare conditions.

**Conclusions**

In our series, the overall prevalence of gonadal tumor in patients with bilateral streak gonads containing Y chromosome material was 56%. Considering the early occurrence of gonadoblastoma and its high potential for malignant transformation, prophylactic gonadectomy is strongly recommended soon after diagnosis.

**References**


