CASE REPORT

Dysgerminoma and Gonadal Dysgenesis in a 46,XX Female with No Evidence of Y Chromosomal DNA

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The occurrence of dysgerminoma in dysgenetic gonads without Y chromosomal influence is exceptionally rare. We used Southern blot hybridization of Y-DNA probes to genomic DNA to search for any Y-related influence in a patient with a dysgerminoma, dysgenetic gonads, and a 46,XX karyotype. No Y-specific DNA was found at 11 loci representing the short arm, centromere, and long arm. This absence of any Y-DNA leaves open to question the absolute requirement of Y-related influence in the development of dysgerminoma in dysgenetic gonads. © 1995 Academic Press, Inc.

INTRODUCTION

Gonadoblastoma and dysgerminoma are the most common ovarian tumors in patients with dysgenetic gonads. Although not a prerequisite, a Y chromosome or mosaicism for the Y chromosome is detected in the great majority of patients with dysgenetic gonads and dysgerminoma. In a review of 26 patients with dysgenetic gonads, dysgerminoma, and identified karyotypes, 25 had Y-chromosomal material (96%); only one pure dysgerminoma with a 46,XX karyotype was identified [1]. These observations strongly suggest that the Y chromosome plays an important role in the malignant changes leading to the development of dysgerminoma in dysgenetic gonads. In these rare cases where an intact Y chromosome was not detected, this genetic influence could potentially have arisen from a fragment of the Y chromosome too small to be detected by conventional cytogenetic studies.

Analogue circumstances prevail in cases of abnormal sexual development where a specific, sex-determining region of the Y chromosome and not the entire, intact Y chromosome is required for testicular development. Although exceptions have been found, data from the study of 46,XX males and 46,XY females suggest that testicular development depends upon the presence of only a very small portion of the Y chromosome [2]. We report a case of pure gonadal dysgenesis, a dysgerminoma, and a 46,XX karyotype in three tissues tested. The rarity of dysgerminoma in this clinical setting and the almost absolute prerequisite of Y influence in the development of dysgerminoma in dysgenetic gonads prompted us to search for Y-specific DNA that might have eluded detection by conventional methods of cytogenetic analysis. This case is only the second reported in the literature and the first in which Y-specific DNA is sought.

CASE REPORT

A 19-year-old gravida 0 was referred for evaluation of an asymptomatic pelvic mass and amenorrhea. The patient underwent an evaluation 1 year earlier for primary amenorrhea and was placed on oral contraceptives without further diagnostic study. She was successfully cycled for 4 months and discontinued the oral contraceptives for nonmedical reasons and without medical consultation. Amenorrhea recurred and the patient again sought evaluation after a hiatus in care of 8 months. Clinical examination at another institution revealed a 7 × 7 × 5-cm cul-de-sac mass confirmed on pelvic ultrasound examination. She was then referred for consultation.

Her past medical history was unremarkable. Significant family medical history included a sister who underwent a total abdominal hysterectomy and unilateral salpingo-oophorectomy at age 12 years for a mature ovarian teratoma. Cytogenetic analysis revealed a 46,XX karyotype. She subsequently was lost to medical evaluation and has not kept in touch with her family.

On physical examination, the patient appeared well. The height was 160 cm and weight was 55 kg. Tanner staging revealed a small amount of areola and papillae above normal breast tissue (stage IV of V) and pubic hair restricted to the mons (stage IV of V). Pelvic examination revealed an irregular 5 × 6 × 7-cm right-sided pelvic mass that filled the cul-

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de-sac and extended to the left of the midline. Laboratory evaluation included assay for serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone, and estradiol of 140 mIU/ml, 45 mIU/ml, and 16 pg/ml, respectively. Serum concentrations of prolactin, testosterone, lactate dehydrogenase, chorionic gonadotropin, α-fetoprotein, CA-125, and carcinoembryonic antigen were within the normal, nonpregnant ranges. Radiologic examinations included pelvic ultrasound and abdominopelvic CT examinations which confirmed a 4 × 4 × 5 cm solid right ovarian mass with an unidentified left ovary.

An exploratory laparotomy was performed. A 4 × 5 × 6 cm solid right ovarian mass and left ovarian streak ovary were found. A right oophorectomy, left ovarian wedge biopsy, lymph node sampling, and partial omentectomy were performed and specimens were forwarded for histologic analysis. Biopsies from the right ovary, left (streak) ovary, and skin were obtained for cytogenetic analyses. Postoperatively blood was obtained for analysis of Y-specific DNA.

Histologic examination of the right ovary revealed pure dysgerminoma and examination of the left ovary revealed fibrous tissue without evidence of malignancy consistent with a streak ovary. Cytogenetic analysis of peripheral lymphocytes with GTB-banding revealed a 46,XX karyotype. Analysis of cells obtained from tissue culture of the left (streak) ovary and skin fibroblasts also revealed a 46,XX karyotype. Tissue from the right (dysgerminoma) ovary failed to grow in culture. Examination of blood DNA for Y-specific sequences was performed as previously described [3]. No Y-chromosomal material was detected on analysis of 11 loci representing the short arm, centromere, and long arm (Table 1).

**DISCUSSION**

In this Case Report we describe a patient with pure gonadal dysgenesis, pure dysgerminoma, and a 46,XX chromosomal complement in all three tissues examined (skin, gonad, and blood). Such occurrence of a dysgerminoma in the absence of Y-chromosomal material is rare [4]. With few exceptions, dysgerminomas in patients with gonadal dysgenesis occur in conjunction with an intact Y chromosome or Y mosaicism, suggesting that one or more Y-chromosomal genes play a causal role in development of this neoplasm. A role for one or more Y-chromosomal genes in the etiology of gonadoblastoma in dysgenetic gonads has been hypothesized [5]. In the only similar case reported, chromosomal analysis was restricted to peripheral lymphocytes where a 46,XX karyotype was observed [6]. A potential influence by Y-specific DNA in the development of a dysgerminoma in dysgenetic gonads has not been investigated.

In the present case, we sought to determine the presence of Y-specific DNA by hybridization with probes derived from the short arm, centromere, and long arm of the chromo-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Southern Blot Hybridization of Y-DNA Probes to Genomic DNAs from the Patient Described and Normal Males and Females</th>
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<tbody>
<tr>
<td>Interval</td>
<td>Probe/locus</td>
</tr>
<tr>
<td>1A1A</td>
<td>pDP120/5R3/RYY</td>
</tr>
<tr>
<td>1A1B</td>
<td>pDP1056/5RP3/RYY</td>
</tr>
<tr>
<td>1A2</td>
<td>pDP101/5R3/RYY</td>
</tr>
<tr>
<td>1A1B</td>
<td>pDP1059/5R1/RYY</td>
</tr>
<tr>
<td>3</td>
<td>502/2/A, B</td>
</tr>
<tr>
<td>3</td>
<td>pDP1059/5R1/RYY</td>
</tr>
<tr>
<td>4B</td>
<td>pDP107/5R1/RYY</td>
</tr>
<tr>
<td>4B</td>
<td>pDP107/5R1/RYY</td>
</tr>
<tr>
<td>5</td>
<td>pDP527/5R1/RYY</td>
</tr>
<tr>
<td>6</td>
<td>502/2/C, E</td>
</tr>
<tr>
<td>7</td>
<td>pY431/5R1/RYY</td>
</tr>
</tbody>
</table>

Note: All DNA probes were hybridized to Southern blots of genomic DNAs digested with the restriction endonuclease EcoRI. H, high stringency (hybridization at 47°C, wash at 65°C); M, medium stringency (hybridization at 42°C, wash at 55°C).
members have been affected with teratomas [7–9]. These prior descriptions and the unique aspects of the present case suggest that under select circumstances factors other than Y-chromosome influence may be operative in the induction of germ cell tumors and question the absolute requirement for Y-chromosomal DNA in the development of the dysgerminoma in this case.

In this Case Report, we describe the development of a dysgerminoma in a dysgenetic gonad in a patient with a 46,XX karyotype in all three tissues tested. This case represents only the second such case reported. With these two exceptions, all prior cases describe Y-related influence in the neoplastic changes. This infrequent clinical scenario and the seemingly absolute requirement of the Y chromosome prompted detailed analyses for Y-chromosomal material not necessarily detected by routine cytogenetic study. This absence of any Y-DNA leaves open to question the absolute requirement of Y-related influences in the development of dysgerminoma in dysgenetic gonads. The family history and previous case reports suggest that under certain circumstances other factors may be involved in the induction of germ cell tumors.

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REFERENCES


