Familial dysgerminoma associated with 46, XX pure gonadal dysgenesis

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ABSTRACT

Although the occurrence of pure gonadal dysgenesis (PGD) is usually sporadic and nonfamilial, here we present 3 sisters with 46, XX PGD, who are born from a first cousin marriage. Review of their family pedigree is compatible with autosomal recessive inheritance. Surprisingly, 2 of these sisters developed ovarian tumors. Both showed the pathological result of dysgerminoma with syncytiotrophoblastic giant cells. These 2 cases are examples of tumorigenesis in PGD without an identifiable Y chromosome. Therefore, malignant degeneration of the streak gonads should be considered in the patients with 46, XX PGD.

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The term pure gonadal dysgenesis (PGD) refers to 46, XX or 46, XY phenotypic females who have streak gonads with primary amenorrhea and sexual infantilism. Affected girls are typically of normal height and have none of the stigmata of Turner's syndrome.[1] Pure gonadal dysgenesis with 46, XX karyotype has been reported in a few familial aggregates.[2] However, dysgerminoma with syncytiotrophoblastic giant cells (SGC) is a rare ovarian tumor.[3] To our knowledge this is the first report of dysgerminoma with SGC associated with PGD in 2 members of a family, who are born from a consanguineous marriage. Chromosomal, endocrine and morphological studies of the affected cases as well as evaluation of their family pedigree were carried out in an attempt to further understand the etiology.

Case Reports. The affected cases were 3 sisters with primary amenorrhea. The other siblings in the family had normal reproductive functions and had been fertile. Their parents were first degree cousins **(Figure 1)**. No cases of reproductive failure was revealed in the previous generations of this family.

Patient One. A 31-year-old woman with primary amenorrhea presented with an abdominal protrusion and 10 kg of weight loss since 8 months prior to admission. Physical examination showed eunuchoidal proportions with height of 159 cm and arm span of 163 cm. She had infantile genitalia, and minimal breast development (Tanner stage 2).[4] In abdominal examination a 25x23x20 cm fixed solid mass could be palpated which had filled the pelvis up to the umbilical area. For chromosomal analysis, peripheral blood leukocytes were cultured. For each karyotype, 50 metaphases were analyzed. Trypsin-Gimsa binding were utilized to detect structural aberrations according to the International System for Chromosome Nomenclature 1995.[5] Her karyotype studies showed normal 46, XX pattern without mosaicism. To perform endocrine studies, serum pituitary gonadotropins (luteinizing hormone and follicle stimulating hormone), estradiol (E2) and beta subunit of human chorionic gonadotropin (ß-hCG) were measured by specific

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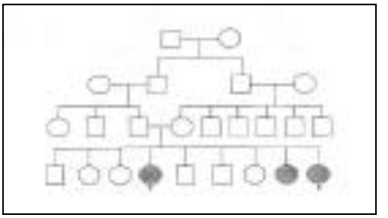

Figure1 - Pedigree of the family with 3 affected siblings with 46, XX pure gonadal dysgenesis. The asterisks show accompanying ovarian tumors.

Table 1 - Laboratory data of the affected cases.

Variables	Patient 1	Patient 2	Patient 3	Normal values in the reproductive ages
LH (IU/L)	34	35.4	34.1	5-20
FSH (IU/L)	56	45.5	112	5-30
Estradiol (Pg/ml)	13.2	18.1	25	30-450
ß.hCG (IU/L)	10	32	2	<5
AFP (µg/L)	4	3	5	<10
CA 125 (U/ml)	25	20.4	15.1	<35

LH - luteinizing hormone, FSH - follicle stimulating hormone, AFP - alfa-fetoprotien, ß.hCG - beta subunit of chorionic gonadotropin, CA 125 - cancer antigen 125

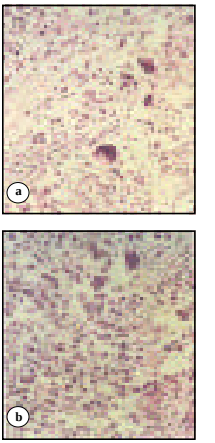

Figure 2 - Microscopic view of the tumors in patient one **(a)** and patient 2 **(b)** with typical dysgerminoma cells and islands of syncytiotrophoblastic giant cells (H & E x20) original magnification.

radioimmunoassay techniques. Serum alfa-fetoprotein (AFP) and CA 125 were also determined by enzyme immunoassay (CangAg, Gothenburg, Sweden). These data are shown in **Table 1.** During laparotomy, a large mass originating from the right ovary was debulked and hysterectomy and lymph node dissection were performed. Microscopically the tumor showed dysgerminoma with SGC with round nuclei, conspicuous nucleoli and pale vacuolated cytoplasm which formed solid sheets, with lymphatic infiltration. The SGC were scattered and had an eosinophilic cytoplasm and numerous uniform nucleoli **(Figure 2).** No normal ovarian tissue with follicles was detected in the specimen. The patient was classified as stage IIIc according to the Federation of International Gynecologists and Obstetricians (FIGO).[6] She received several courses of chemotherapy and radiotherapy. Now in 15 months follow up after her operation she has no sign of recurrence and is well.

Patient 2. A 22-year-old woman with primary amenorrhea presented with an abdominal protrusion and mass sensation for 4 months prior to referral. Physical examination disclosed a female 160 cm tall with an arm span of 169 cm. She had infantile genitalia with under developed breasts (Tanner stage 2).[4] A 19x15 cm pelvic mass was palpated. She had normal 46, XX karyotype. Her endocrine studies are included in **Table 1.** During laparotomy, a large mass had involved her right gonad. Her uterus was atrophic with a left sided cordlike gonad. Resection of the right gonadal tumor and the left streak gonad was performed. Microscopically the tumor showed dysgerminoma with SGC **(Figure 1).** The streak gonad was a fibrous structure without follicles. The patient was classified as stage Ia according to FIGO.[6] Now after a 12 month follow up the patient is well.

Patient 3. A 26-year-old woman with primary amenorrhea, 166 cm tall and arm span of 174 cm. She had small breasts (tanner stage 2) and infantile genitalia, without any other somatic abnormality. A tiny uterus could be palpated in rectal examination. Her karyotype studies showed 46, XX. Ultrasound (US) also computerized tomographic (CT) scanning of her abdomen and pelvis showed a small uterus measuring 4x2x2 cm. The right and left ovaries were 2x1.5x2 cm and 1.8x1.6x1 cm. No tumoral involvement could be detected by the above studies.

Table 1 shows her laboratory data. Prophylactic oophorectomy was suggested to her, but she has refused this procedure, to date. Therefore, periodic physical examination and ultrasound evaluation are being performed for her.

Discussion. Our patients were phenotypically female with primary amenorrhea and eunuchoidal proportions they had normal neurological development. All of them had hypergonadotropic hypogonadism with 46, XX karyotype. In the 2 operated cases the histopathological data were in favor of streak gonads, confirming the diagnosis of PGD. The family pedigree supports the existence of an autosomal recessive form of gonadal dysgenesis which has been previously reported.[7]

Although general agreement exists that gonadal dysgenesis with Y chromosome is associated with high incidence of gonadal tumor, the increased risk of tumor in gonadal dysgenesis without a Y chromosome is less clear. There are several reviews of the world literature on neoplasms in dysgenetic gonads showing that approximately 4.2-22% of tumors had developed in the patients without a Y chromosome.[8,9] Our patients had 46, XX karyotype and ovarian tumors developed in 2 of them. Absence of a chromosome Y in their peripheral blood does not eliminate the possibility of mosaicism with a Y chromosome containing cell line. We did not have the facilities to evaluated the presence of sex-determining region Y (SDR-Y) in the tumor DNA in our center. However, in a recent sporadic similar report, SDR-Y could not be detected in the tumor DNA.[3] It seems that in such cases the genetic information responsible for malignant degeneration of dysgenetic gonads may have been translated to an autosomal chromosome. It is stated that high gonadotropin levels in these patients stimulate the ovarian cells for malignant degeneration.[10]

From a statistical stand point, the incidence of PGD is estimated to be approximately 1/4500.[11] A woman's risk at birth of having dysgerminoma sometime in her life is nearly $1.5\text{-}4.5 \times 10^{4}$.[12] With consideration of the fact that SGCs are present only in 3% of dysgerminomas,[2] the chance of their coincidental occurrence is therefore $1\text{-}3 \times 10^{9}$. We believe that this rare condition happened in our cases secondary to an autosomal recessive gene which, could have been probably stimulated by a common environmental factor.

From a practical point of view, it can be concluded that absence of a Y chromosome in patients with PGD should not induce a false sense of security. Therefore, periodic surveillance of patients with 46, XX PGD is suggested for early diagnosis of the possible neoplastic changes.

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