Dysgerminoma in a female with Turner syndrome and Y chromosome material: A case-based review of literature

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ABSTRACT

We report a 17-year-old girl evaluated for primary amenorrhea. Cytogenetic analysis of the peripheral blood lymphocytes revealed normal autosomes with 46X inv (Y) confirming the diagnosis of Turner’s syndrome with Y cell line. Treatment was initiated with conjugated estrogen while recommending bilateral prophylactic oophorectomy to the patient. One year later the patient presented with abdominal mass, biopsy of the specimen following resection confirmed dysgerminoma originating from right ovary with no invasion or metastasis. The literature is reviewed with regard to the various pathogenetic mechanisms proposed for the development of germ cell tumors in ovary, the cytogenetic findings and recommendations to handle such scenario.

Key words: Dysgermonoma, gonadal dysgenesis, gonadoblastoma, mosaicism, Turner’s syndrome, Y cell line

INTRODUCTION

Turner’s syndrome (TS) is one of the most common chromosomal aneuploidy and is present in 1:2000 to 1:2500 live births.[1] It is a disorder caused by partial or complete X-chromosome monosomy and characterized by short stature, ovarian failure, and specific somatic abnormalities.[2] Approximately 40-60% of patients with TS have 45XO karyotype, while remaining subjects have a chromosomal abnormality of X-chromosome including severe mosaicism.[3] Normal or a structurally abnormal Y-chromosome or Y-derived sequences in TS individuals is found in 6-9% cases.[4] Early detection of Y-derived sequences is of great importance because of the high risk (10-30%) of developing gonadal tumors.[5] Gonadoblastoma and dysgerminoma are the most common malignant tumors of the dysgenetic gonads.[6] At times the gonadoblastoma can undergo transformation into invasive dysgerminoma in 60% cases and also into other malignant forms of germ cell tumors.[7] Prophylactic gonadectomy should be recommended in patients with TS and Y-chromosome mosaicism.[8]

CASE REPORT

A 17-year-old female was evaluated for primary amenorrhea. She was borne to parents of nonconsanguineous marriage, delivered at term with an uneventful birth history. Physical and mental milestones and developmental history throughout the infancy and childhood was normal. There was no history of headache, vomiting, seizures, chronic illness, any drug/radiation exposure. She was the second child of her parents with normal elder brother.

On examination patient appeared to be in good general
health and a height of 155.5 cm, weight of 59 kg. She had no midline deformity or stigmata of TS. She had Tanner stage 1 breast and pubic hair development. On pelvic examination she had hypoplastic external genitalia. Systemic checkup including abdominal and cardiovascular examination was normal.

Routine hematology, urine analysis was normal. Bone age determined by Greulich and Pyle was 11 years. Hormonal evaluation revealed FSH - 46.5 IU/L (N-1.2-13.2), LH - 60.6 IU/L (N- 4.9-14.5), estrogen - 4.0 pg/ml (N-19.0-111), prolactin 37 ng/ml (N-0.9-14.1). Hormonal tests for other anterior pituitary functions were within normal limits. Ultrasonography revealed a hypoplastic uterus (2.0 × 2.0 × 1.1 cm) with small ovaries (right 2 cm and left 1.9 cm). The chromosomal study of peripheral blood lymphocyte with G-T-G banding in 20 analyzed metaphases revealed normal autosomes and abnormal sex chromosomes in the form of 46X inv (Y) [Figure 1]. Treatment with conjugated estrogen (0.01 mg) was started. The patient was advised for prophylactic bilateral oophorectomy after explaining about the potential malignant risk.

Examination at follow-up after 12 months revealed adequate breast development and growth of axillary and pubic hairs (B III, P III, A III). There was no menarche. On abdominal examination there was an non tender, ovoid 8 × 7 cm mass, solid in consistency and freely movable, in lower abdomen and pelvis. Ultrasonography revealed a large, solid, lobulated mass with irregular internal echogenicity emanating from right ovary [Figure 2]. The patient was subjected to laparotomy and a smooth and bosselated tumor of 11 × 10 × 7 cm was removed from right ovary. No metastases were evident. Histopathology of the biopsy specimen revealed uniformly appearing large, round cells with vesicular nuclei and clear or finely granular cytoplasm that is eosinophilic admixed with lymphocytes in the stroma, confirming the diagnosis of dysgerminoma [Figure 3]. Postoperative course was uneventful and the patient was discharged 4 days later.

**Discussion**

In the present case dysmorphic features of TS were not found. Guedes et al. also studied a girl who despite her 45X/46X, der (Y) karyotype displayed no features of TS except for decreased growth speed. Our patient had only the features of delayed bone age. Except for short stature, all other findings are inconsistent. Possible explanation might be undetected mosaicism, since diagnosis is usually made by analyzing between 5-30 peripheral blood lymphocytes to determine the karyotype and the second line is often present as a proportion of no more than 1-2% of the

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**Figure 1:** Karyotype of the patient - normal autosomes and abnormal sex chromosomes in the form of 46X inv (Y)

**Figure 2:** Ultrasonography of abdomen: large, solid, lobulated mass with irregular internal echogenicity emanating from the right ovary

**Figure 3:** Histopathology of the biopsy specimen - large, round cells with vesicular nuclei and clear or finely granular cytoplasm that is eosinophilic admixed with lymphocytes in the stroma, confirming the diagnosis of dysgerminoma (H and E, ×300)
Dysgenetic gonads serve as the risk factor for origin of germ cell tumors.\textsuperscript{15} Patients with disorders of sexual development carry an additional risk. The precursor lesion in a dysgenetic gonad is gonadoblastoma, which has the potential to progress toward invasive germ cell tumors, particularly dysgerminoma and less frequently embryonic carcinoma, teratoma, yolk sac tumor, and choriocarcinoma.\textsuperscript{16} Hyperandrogenism is commonly associated with gonadoblastoma, especially in cases of coexistence with dysgerminoma.\textsuperscript{17} Our patient had no such features. GBY (gonadoblastoma locus on the Y chromosome) is assumed to be related to the origin of tumors located in the pericentromeric region of Yp.\textsuperscript{18} It is different than the testis determining region (SRY). SRY is located proximally while GBY is located distally. Germ cell tumors (GCT) are more common in whom the Y-chromosome retains the normally intense florescence of distal Yq. Gonadal dysgenesis is due to the presence of Y-chromosome lacking the male determining region (SRY).\textsuperscript{19} SRY is suggested to be functional in spermatogenesis\textsuperscript{20} and is the structural gene for H-Y antigen. H-Y antigen is an oncogene, and seems to be closely associated with development of GCTs.\textsuperscript{21} Low occurrence of GCT in Turner females with Y-chromosome material might be related to the lower level of H-Y antigen found in Turner syndrome.\textsuperscript{22} The lack of a regulatory Y-chromosome gene or genes on the X-chromosome, which may influence the level of H-Y antigen or other potential carcinogenic oncogenes might be the reason why Y-chromosome material in TS seems to cause the development of GCT to a much lesser degree than in XY females.\textsuperscript{23} Salo et al. have identified TSPY (tissue-specific protein Y encoded) as a candidate gene for GBY locus related to development of GCT.\textsuperscript{23} Furthermore immune reactivity of POU5F1 (OCT 4) gene at 6p 21.31 is found to be positive for GCTs. Other studies have established the presence of Y-chromosome sequences like PABY (Y-chromosome pseudoautosomal bound region 1), SRY, ZFY (Y-chromosome-specific zinc finger gene), Yc (Y-chromosome centromeric alphoid region), and Yq (Y-chromosome long-arm heterochromatic region) as risk factors for GCT.\textsuperscript{24} Germ cells persist for longer time in the dysgenetic gonads of XY female than in gonads from 45X patients. Germ cells obviously have increased potential for malignancy in certain environment.\textsuperscript{25}

It has traditionally been recommended that a search for Y-chromosome fragments in TS should only be performed under two circumstances: when there are signs of virilization and/or when there is a marker chromosome not identified by classical cytogenetics.\textsuperscript{26} Nevertheless, when Canto et al.\textsuperscript{27} used PCR to study 107 Turner syndrome patients with a 45, X karyotype, they identified Y-chromosome material in 10 (9.3\%) of them. Prophylactic gonadectomy was indicated, and two of the six patients who agreed to undergo the surgery presented gonadoblastoma, thus indicating an incidence of 33\%.

Similarly, Bianco et al.\textsuperscript{14} studied different tissue samples from 20 TS patients by means of PCR and found that seven (35\%) of the 45, X patients presented Y-chromosome-specific sequences in at least one of the tissues studied. Four (14\%) of these patients underwent prophylactic gonadectomy, and bilateral gonadoblastoma was found in a 16-year-old girl. In this case, the presence of Y-chromosome sequences was not associated with virilization, thus reinforcing the idea that the absence of this characteristic does not rule out the possibility of the presence of hidden Y-chromosome fragments.

Prevalence of GCT in Y-chromosome varies among different studies pegged at 10-30\%.\textsuperscript{8} So prophylactic gonadectomy is recommended in such patients.\textsuperscript{8} But Gravholt et al. have questioned this consensus on basis of their finding of frequency of Y-chromosome material in TS as 12.2\% with occurrence of gonadoblastoma among Y-positive patients as 7-10\%.\textsuperscript{9} They recommended detailed vaginal sonography with color doppler sonography of gonads at regular intervals. But they go on to conclude that gonadectomy is still the procedure of choice to exclude malignancy with absolute certainty. However, as most of the studies have found higher incidence of GCT to the tune of 30-35\%,\textsuperscript{10} we thought it suitable to recommend prophylactic gonadectomy to our patient. The male genotype can exist as XY, XYY, a partial Y-chromosome such as dicentric Y, a ring Y or even a Y translocated to another chromosome.\textsuperscript{28}
The mean age of gonadal tumor diagnosis as per previous reports is 18 years.[29] Our patient was 17 years old. Virilization in patients with TS indicates the presence of Y cell line within the gonads, even if Y cell is not identified in the peripheral blood. So virilization is an indication for the presence of Y mosaicism.[30] Our patient had no virilizing features. A few times, the gonadal tumor has been reported without evidence of Y-chromosome.[31] The basis was dysgenetic gonad itself giving rise to GCT. It leads to the suggestion that laparoscopic and ovarian biopsy might be considered in any patient suspected of dysgenetic or dysplastic ovaries.

**Conclusion**

Early detection of Y-chromosome sequence in TS is of great importance because of high risk of gonadal tumor development. Though the occurrence of Y-chromosome material in TS is low, it should be searched meticulously by molecular techniques like FISH, PCR. Since most studies have indicated 30-35% incidence of GCTs, prophylactic gonadectomy should be offered to TS patients with Y-chromosome.

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