Laparoscopic gonadectomy in a case of a dicentric fluorescent Y-chromosome mosaicism with Turner-like phenotype and virilized external genitalia

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Summary

In few cases of Turner syndrome the karyotype reveals the presence of an additional Y-bearing cell line, which is referred to as a borderline case of mixed gonadal dysgenesis. We report a 20-year-old woman with primary amenorrhea, virilization and a few Turner stigmata, who revealed rare mosaicism of 45,X/46,X dic (Y; 5)(q12; q11), +5/46,X, der (Y), which was detected by conventional G-banding and multicolor spectral karyotyping. She underwent laparoscopic gonadectomy in which mixed gonadal dysgenesis was found and both gonads were removed. No evidence of gonadoblastoma was noted on the gonads. Virilization improved postoperatively. We recommend gonadectomy via laparoscope in women presenting with Turner-like phenotype, virilization and the presence of a Y chromosome. This report describes the role of cytogenetic and molecular genetic investigations in the definition of mosaicism in Turner syndrome.

Key words: Mixed gonadal dysgenesis; Turner syndrome; Spectral karyotyping; Laparoscopy.

Introduction

Turner syndrome is the most frequent cause of ovarian regression. While the etiology of this syndrome is mainly due to monosomy X, mosaicism with at least one additional cell line results in a broad spectrum of phenotypes depending on the nature of the second cell line with another normal or rearranged sex chromosome. Individuals with Y chromosome material in their genome present with many phenotypes, ranging from normal male to phenotypic female, often with mixed gonadal dysgenesis and virilization, and bear a significantly increased risk of development of gonadoblastoma. For that reason, it is crucial to evaluate if a putative Y chromosome is Y origin, since consideration must be given to prophylactic gonadectomy in order to prevent the development of malignancy [1, 2]. Although this can be done with conventional G-banding, cytogenetic analysis provides critical information of diagnostic and prognostic importance for gonadal dysgenesis.

In this report we describe a case in which laparoscopic gonadectomy were performed in a woman who had Turner-like phenotype with mixed gonadal dysgenesis as well as virilized external genitalia and rare structural abnormalities of the Y chromosome, which was detected by multicolor spectral karyotyping.

Case Report

The patient was a 20-year-old woman who presented to her outside physician with primary amenorrhea. She had a history of surgery for a coarctation of the aorta at eight years old. She reported that she had a minimal amount of breast tissue, and she did not remember when that had started. She was otherwise healthy, using no medications. She was in the second year of university, and her motor and mental development were normal. Her family history was unremarkable. Her height was 143.1 cm, and she weighed 56.3 kg. No thyromegaly was present. Her breasts were Tanner Stage I. Besides her short stature, she exhibited a few indistinct Turner stigmata: broad chest, widely spaced nipples and slight cubitus valgus. The external genitalia were female with an enlarged clitoris and male-type pubic hair. Pelvic ultrasound revealed a small uterus without detectable endometrium. The ovaries were not demonstrated.

Endocrinological laboratory tests showed a FSH level of 56.9 mIU/ml, LH level of 37.5 mIU/ml and testosterone level of 167 ng/dl (normal range: 10~85 ng/dl), which were clearly increased for a 20 year-old female, and low estradiol level (3.5 pg/ml).

Chromosomal examination of blood lymphocytes was initially performed by GTG (G-bands by trypsin using Giemsa) and revealed mosaicism 45,X/46,X, +mar1/46,X, +mar2 with 45,X being the predominant line (19 out of 30 cells). The distribution of the second and third cell line was 9 and 2 out of 30 cells, respectively. To investigate the presence of Y chromatin, spectral karyotyping (SKY) [3] based on the hybridization of 24 fluorescently labeled chromosome painting probes showed the dicentric nature of the abnormal Y-chromosome in the second cell line. The SKY failed to delineate unambiguously the chromosomal origin of another marker chromosome due to the small size of the marker in the third cell line. The karyotype was finally interpreted as 45,X/46,X dic (Y; 5)(q12; q11), +5/46,X, der (Y).

Laparoscopic removal of the gonads was performed, because Y-chromosomal material was found in her genome. The right gonad was identified, and the small but apparent uterus and bilateral fallopian tubes were seen. The left gonad looked like a "streak". Bilateral gonadectomy was performed. On pathological examination, the left gonad consisted of fibrovascular con-

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nective tissue with rete ovarii. The right gonad showed well-formed immature seminiferous tubules in loose mesenchymal tissue. The tubules were wholly composed of Sertoli cells without spermatogonia. The stroma contained a small aggregate of eosinophilic cells resembling Leydig cells. There was no evidence of gonadoblastoma. The level of testosterone decreased to 30 ng/dl four weeks after the gonadectomy.

Discussion

Turner syndrome is the major cause of primary amenorrhea, and usually suspected from the constant finding of short statue in association with webbed neck, cubitus valgus, low hairline and the lack of pubertal development associated with gonadal dysgenesis. However, if a Y bearing cell line is present in addition to the 45,X line, the resulting phenotype may show different degrees of virilization [4], and can be interpreted as a variant of mixed gonadal dysgenesis.

Our patient is a woman with primary amenorrhea, short stature and other stigmata of Turner syndrome. An enlarged clitoris and male-type pubic hair indicated virilization. While pelvic ultrasound or magnetic resonance imaging of the gonads may reveal dysgenetic structures, their absence as seen in this case is not a reliable indicator of the risk of gonadoblastoma. It is, therefore, necessary to identify or exclude the presence of Y chromosome material, in order to provide appropriate advice for clinical management. G-banding and SKY revealed the karyotype 45,X/46,Xdic (Y; 5)(q12; q11), +5/46,X, der (Y) with a slightly prevailing 45,X cell line. The 45,X cell line in this case is of more influence on the phenotype than the presence of Y chromosomal material.

The risk of gonadoblastoma is difficult to quantify. Krasna *et al.* [4] suggest that the presence of a Y chromosome or part of a Y chromosome is associated with a 25-70% risk, the highest risk being associated with mixed gonadal dysgenesis and increasing age. Hsu [5] reviewed 44 cases with a dicentric Y chromosome and suggests that in patients with postnatally diagnosed 45,X/46,XY karyotype, the risk appears lowest in phenotypic males, intermediate (0.5%) in patients with ambiguous external genitalia and highest (22%) in phenotypic females. These risks are almost certainly underestimated as many patients have been assessed at a relatively young age. In the present case, gonadectomy was indicated by the presence of obvious virilization and her advanced age, and revealed tubular formations without evidence of gonadoblastoma. The postoperative decrease in the serum level of testosterone suggested that testosterone was produced by the gonads in the present case.

It is suggested that a woman with Turner-like phenotype and virilization should have further analyses with cytogenetic studies in addition to routine peripheral blood chromosome analysis, in order to confirm the presence of Y chromatin and to identify structural abnormalities of the Y chromosome. The likelihood of dysgenetic gonads should be investigated by laparoscopy, and if gonadectomy is indicated it should be performed as early as possible to prevent malignant change and treat virilization.

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