

## DYSGERMINOMA IN A PATIENT WITH PARTIAL DELETION OF X CHROMOSOME

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Abnormalities involving the X chromosome have been well described. Complete monosomy X results in Turner's syndrome. The effects of partial monosomy of the arms of the X chromosome depend on the location of the breakpoint in the arms. Accordingly, individuals affected may or may not have Turner phenotype, with or without gonadal development or function. The patients who have gonadal dysgenesis are at increased risk of development of germ cell tumors.<sup>1</sup> Gonadoblastomas are the most frequently occurring germ cell tumors in dysgenetic gonads with Y chromosome.<sup>1,2</sup> Other germ cell tumors that have been reported include embryonal cell carcinoma, mucinous cystadenoma and in rare instances, dysgerminoma.<sup>3,4</sup>

### Case Report

A 12½-year-old Caucasian female presented with a long history of abdominal pain, nausea and constipation, which was relieved by laxatives. The father had accidentally felt a mass in her lower abdomen, which prompted him to seek medical attention for her. She had been born at term, vaginally, after an uneventful pregnancy resulting from a nonconsanguineous marriage. She had normal growth development and good school performance but had not attained menarche. Physical examination revealed a height of 148.7 cm (10th percentile) and a weight of 64.3 kg (>90th percentile). She had shortening of the left third, fourth and fifth toes, and the third and fifth toes on the right side. Her abdomen was protuberant, with liver and spleen palpable 4 cm below the costal margins and a large, firm and tender mass in the left lower quadrant.

Imaging studies revealed a large abdominopelvic mass with calcification extending along the para-aortic region to

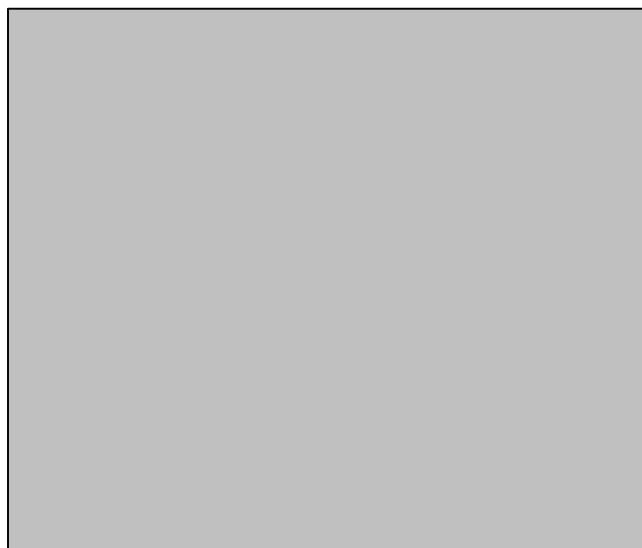


FIGURE 1. Constitutional karyotype showing 46,X,del(X)(q21.1). The same karyotype was found from a tumor tissue culture preparation.

the tracheal carina. The mass appeared to be arising from the left ovary. There was dilatation of the left extrarenal pelvis and mild hydronephrosis. Metastatic workup revealed no disease elsewhere. The biopsy of the abdominal mass was reported as dysgerminoma. B-HCG levels were significantly elevated at 64 MIU/mL (normal in non-pregnant females <10 MIU/mL). AFP levels were normal. Karyotyping of the biopsy specimen showed del (X) (q21.1). This was also observed in peripheral blood karyotyping, confirming a constitutional abnormality (Figure 1).

Since the mass was unresectable, the patient was started on chemotherapy with vincristine, adriamycin, cyclo-phosphamide and DTIC, to which she responded with dramatic reduction in the size of the mass and normalization of B-HCG levels. She received 4 courses of the above regimen at three-week intervals, after which she was changed to another regimen with bleomycin, etoposide and cisplatin at three-week intervals, for a total period of 16 weeks. Repeat re-evaluation showed no evidence of disease in the chest, but the abdomen showed calcified

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para-aortic nodes and soft tissue densities in the areas of the primary tumor. B-HCG values were within normal limits. She also had endocrinology evaluation at diagnosis, which showed elevated FSH, LH, TSH, prolactin, low T4, FTI and normal T-uptake.

Since she would not be able to conceive unless artificially implanted with an embryo and due to the increased risk of tumor in her streak ovaries, she underwent salpingo-oophorectomy and hysterectomy. Five years after therapy she continues to do well on hormone replacement.

### Discussion

Structural abnormalities of the X chromosome produce partial monosomy of p or q arms or both. Our patient had deletion of the long arm of one X chromosome at the q21.1 locus, resulting in a karyotype 46,X,del (X) q21.1. This karyotypic abnormality was detected first in the tumor cells and then in peripheral blood cells, confirming a constitutional abnormality. All patients with this karyotypic abnormality will have gonadal dysgenesis resulting in sexual infantilism, amenorrhea and sterility, but only one-half will show clinical features of Turner syndrome.<sup>5</sup> Deletion distal to X q22 results in pure gonadal dysgenesis.<sup>5</sup> Our patient had shortening of the 4<sup>th</sup> right finger and left toe due to short metacarpals and metatarsals, which are seen in 16% of the patients with the above karyotypic abnormality.<sup>6</sup> She also had bilateral streak ovaries. No other features commonly described in Turner syndrome were observed, in keeping with the fact that phenotypic variation correlates with structural abnormalities of the X chromosome.<sup>5</sup>

There is a high risk of neoplasm in dysgenetic gonads. Germ cell tumors occur at a much higher frequency in subjects with gonadal dysgenesis associated with presence of a Y chromosome or structural abnormalities of the X chromosome (as noted in this patient).<sup>1</sup> However, Hasle et al. did not find a single case of gonadoblastoma or dysgerminoma in 29 women with Turner's syndrome who had Y chromosome, or in women who had Y chromosome material detected by standard cytogenetic methods, suggesting that the risk of ovarian germ cell tumors may be lower than previously estimated.<sup>7</sup> Gonadoblastomas are the most commonly described germ cell tumors in dysgenetic gonads with Y chromosome.<sup>1,8</sup>

Pierga et al. have described a case of dysgerminoma in a pure 45, X Turner syndrome.<sup>9</sup> The presence of Y material was ruled out by an extensive molecular analysis of the blood and the tumor tissue in our patient. There are no reports in the literature of patients with partial monosomy X and dysgenetic gonads developing dysgerminomas. It appears then that a complete expression of monosomy is not mandatory for the development of germ cell tumor.

Gonadoblastomas tend to give rise to malignant germ cell neoplasms, including dysgerminomas. However, only 50% of the dysgerminomas arise in abnormal gonads and may be associated with gonadoblastomas when they occur in abnormal gonads.<sup>10</sup> Pickel and Tscherne have described two patients who developed dysgerminomas in gonadoblastomas.<sup>3</sup> All stages of evolution of dysgerminomas from germ cells in gonadoblastomas were observed. A unique combination of an ovarian gonadoblastoma, dysgerminoma and mucinous cystadenoma in a patient with Turner's syndrome was reported by Van del Bijl et al.<sup>2</sup> It is unclear whether dysgerminoma was the *de novo* tumor in this patient or developed from a gonadoblastoma. However, there was no evidence of gonadoblastoma in the biopsy specimens and a sampling error cannot be totally ruled out.

It is thought that poorly differentiated gonadal tissue has a propensity for neoplastic transformation and this is conferred by the gene that produces gonadal dysgenesis and germ cell absence. The risk is higher when there is a Y chromosomal cell line in mosaic Turner and gonadal dysgenesis.

Dysgerminoma is a highly radiosensitive tumor and commonly treated with combined surgery and radiation. Since the tumor was unresectable in this patient, she was treated with combination chemotherapy and had an excellent response. She then underwent a second-look surgery to detect viable tumor.

In addition to the risks of malignancy, gonadal dysgenesis is also the most common cause of primary amenorrhea. Our patient did not attain menarche and is currently on estrogen replacement therapy after salpingo-oophorectomy and hysterectomy. Developments in the area of *in vitro* fertilization, embryo transfer and establishment of pregnancy in the absence of ovaries mandate knowledge of the childbearing wishes of the patient before hysterectomy is performed.

It is imperative that any child found to have clinical features suspicious of Turner's syndrome should have cytogenetic and molecular analyses, endocrinology evaluation and gonadal assessment. If dysgenetic gonads are found with Y cell line in phenotypic females, bilateral gonadectomy should be strongly considered in view of the known high incidence of gonadal malignancy in these patients. It is also mandatory to screen the siblings of a patient diagnosed with gonadal dysgenesis and malignancy for similar abnormalities.

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