Treatment of high risk Sertoli-Leydig cell tumors of the ovary using a gonadotropin releasing hormone (GnRH) analog

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Sertoli–Leydig cell tumors are rare ovarian neoplasms. We report two unusual cases with bilateral SLCTs suggesting evidence of genetic predisposition and at high risk of recurrence. To reduce this risk, we exploited the use of GnRH analog to lower gondadotropin and potentially directly inhibit the tumors through expressed GnRH receptors. We used it as maintenance antitumor therapy for 2 years after completion of chemotherapy, to cover the period of risk for recurrence. Both patients remain in complete remission at >2 years after completing leuprorelin therapy. Of note, both patients carry DICER1 mutations, frequently found in pleuropulmonary blastoma syndrome. Pediatr Blood Cancer 2013;60:E16–E18.

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acetate according to the same schedule as case 1 after completing
four courses of chemotherapy. The interval between injections
was reduced to 6 weeks in order to keep LH and FSH levels fully
suppressed. She completed 2 years of this therapy and hormone
replacement therapy was commenced similar to case 1. She
remains in complete remission at 4 years from diagnosis and
30 months after completion of GnRH therapy. The one abnormal
inhibin A level measured during follow up was ascribed to a
laboratory error and subsequent levels were normal (Fig. 1B).

Detection of GnRH Receptors

The receptor binding studies were conducted on frozen tumor
from case 1 [6]. Membranes from a HEK293 cell line stably
expressing the GnRH receptor (SCL60) and rat pituitary were
used as positive control and liver membranes as a negative control. Two separate samples of Case 1 tumor showed specific binding
of radiolabelled GnRH analog as did SCL60 and pituitary
(Fig. 1C and D).

DISCUSSION

There are few data in the literature on risk-adapted therapeu-
tic strategies in ovarian sex cord stromal cell tumors in children.
Schneider et al. [4] described 54 cases documented prospective-
ly and defined risk groups with respect to stage; completeness
of resection; histologic appearance, such as differentiation and
proliferative activity of the tumor. Surgery remains the mainstay
of initial management. Cisplatin based chemotherapy constitutes
an important role as adjuvant therapy for those patients with
SLCT stage I, poorly differentiated and those containing heter-
ologous elements.

In 1975, Stadel [7] proposed the “gonadotropin theory,” hy-
opthesizing that exposure to high gonadotropin levels favor ma-
lignant transformation. SLCTs express receptors for follicle
stimulating hormone (FSH) which has been shown to support
the growth of granulosa cell tumors in nude mice [8]. GnRH
analog therapy at high doses can act to suppress the receptor
activity and has been suggested as treatment for progressive ovar-
ian tumors that have failed to respond to chemoradiation [9]. The
apparent efficacy of GnRH analog in our SLCT patients which
lowered gonadotropins may support this theory. There may have
also been direct antiproliferative effects as described in a number
of reproductive tissue cancers, including ovarian cancer [10–15].
Although there are case reports about the use of GnRH analog for
SLCTs of the ovary in adults [16], no data have been reported in
children. Whilst we could not demonstrate tumor response in the
absence of measurable disease or raised tumor markers, we are
encouraged by the duration of clinical remission in both patients
and their lack of problems on introduction of hormone replace-
ment therapy.
Recent advances in the understanding of the genetics of SLCTs have provided insight into the unusual clinical phenotype in the two cases presented here. Both were included in a study of the rare pleuropulmonary blastoma syndrome of which SLCTs have recently been shown to form part of the spectrum [17]. This syndrome is due to constitutional heterozygous mutations in the DICER1 gene, the master regulator of micro RNA production. Both cases presented had constitutional DICER1 mutations. DICER1 mutations can cause a range of phenotypes from asymptomatic to various tumors such as cystic nephroma, pleuropulmonary blastoma, thyroid cysts, SLCTs, and Wilms tumor. Case 2 also has thyroid cysts, now recognized as part of the DICER1 syndrome [17].

In conclusion, the prolonged remission in two cases presented here suggests that GnRH analogs may have a therapeutic role in high risk SLCTs. While we do not have direct evidence for the efficacy of GnRH analogs with potential influence of high dose therapy and stem cell rescue on case 1, our findings set the scene for further studies for maintenance therapy using GnRH analogs in SLCTs.

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Fig. 2. Case 1 left side tumor [H&E 200×] showing solid nests, cords of Sertoli cells with clusters of Leydig cells (A) and its inhibin staining (B) [inhibin 400×]. Case1 para aortic lymph node [H&E 200×] deposit [14 months later] predominant Sertoli cell features, with small tubules and cords in a hyalinised background and occasional incorporated larger “heterologous” glandular elements with retiform areas (C) [consistent with metastasis from the original right ovarian tumor that had shown similar features]. Case 2 left side tumor [H&E 100×] cells with a partly retiform arrangement in a loose stroma and intermingled clusters of Leydig cells (D) and its inhibin staining (E) [inhibin 200×]. Case 2 right side tumor [H&E 200×]-loose sheets of Sertoli cells and sparse interspersed Leydig cells (F).