

Juvenile Granulosa Cell Tumors: Immunoreactivity for CD99 and Fli-1 and EWSR1 Translocation Status. A Study of Eleven Cases



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Abstract

Background: The accurate diagnosis of a juvenile granulosa cell tumor (JGCT) can be challenging, as these neoplasms often exhibit morphologic features which overlap other ovarian neoplasms. Additionally, the immunohistochemical profile exhibited by JGCTs is fairly non-specific and may include reactivity with CD99. Recently, we noted that JGCTs can show strong immunohistochemical expression of Fli-1, a transcription factor expressed by Ewing sarcoma, a neoplasm which is occasionally in the differential diagnosis with JGCT. We evaluated a series of JGCTs, to determine whether Fli-1 is commonly expressed by these tumors, and whether or not they demonstrate chromosomal rearrangements in *EWSR1*. **Design:** Cases diagnosed as JGCT (n=11) were immunohistochemically evaluated for the expression of Fli-1 and CD99. Fluorescence in situ hybridization (FISH) was performed on all cases to look for chromosomal rearrangements involving *EWSR1*.

Results: All eleven of our cases exhibited positive immunohistochemical staining for Fli-1 and CD99. None of these cases demonstrated a rearrangement in *EWSR1* by FISH.

Conclusions: In cases of JGCT which cannot be reliably distinguished from Ewing sarcoma based on morphology and immunohistochemistry alone, FISH testing for *EWSR1* rearrangements can be a useful diagnostic adjunct for their separation.

Introduction

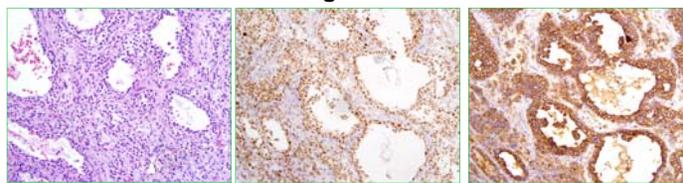
Juvenile granulosa cell tumors (JGCTs) are rare sex-cord stromal ovarian tumors which usually occur in women younger than 30 years of age, with half of them occurring in the first decade of life. Although the majority of Stage IA tumors have an excellent prognosis with a high cure rate, advanced stage tumors (Stage II or greater) are usually fatal.¹ Diagnosing these tumors is often difficult; their morphologic features overlap with many other ovarian neoplasms, and they are often mistaken for malignant germ cell tumors. Immunohistochemical staining can be helpful; however, the immunoprofile of JGCTs can overlap with other entities in the differential diagnosis. There is currently no molecular testing utilized as a diagnostic adjunct for these tumors.

Recently, during diagnostic workup of ovarian tumors in our practice, we have noted positive immunohistochemical staining of JGCTs for Fli-1. Fli-1 (Friend leukemia integrin-site 1) is a transcription factor which is normally present in endothelial cells and small lymphocytes; Fli-1 is a very sensitive marker for Ewing sarcoma/PNET (occasionally in the differential diagnosis for JGCTs)² and is also expressed in vascular tumors, merkel cell carcinoma and melanoma.^{3,4} Its expression in granulosa cell tumors (adult or juvenile) has not been previously described. In the current study, we evaluated a series of JGCTs, to determine the frequency of Fli-1 immunohistochemical expression by these tumors, and whether or not they demonstrate chromosomal rearrangements in *EWSR1* (characteristic of Ewing sarcoma/PNET).

Materials and Methods

Eleven total cases diagnosed as JGCT were identified in the pathology archives at the University of Utah School of Medicine, the Primary Children's Medical Center of Utah, and the David Geffen School of Medicine at UCLA. **Immunohistochemistry:** In each case, immunohistochemical staining for both CD99 (clone O13; Signet; Dedham, MA) and Fli-1 (C-19, Santa Cruz Biotechnology; Santa Cruz, CA) was performed a representative 4-micron thick section of formalin-fixed, paraffin-embedded tissue. ***EWSR1* Fluorescence In Situ Hybridization (FISH):** Each case was tested for *EWSR1* gene rearrangement by FISH using the LSI *EWSR1* Dual Color Break Apart Probe (Abbott Molecular; Abbott Park, IL). Probe signal configurations were enumerated for 100 tumor nuclei. Samples with $\geq 25\%$ rearranged nuclei were considered positive for *EWSR1* gene rearrangement.

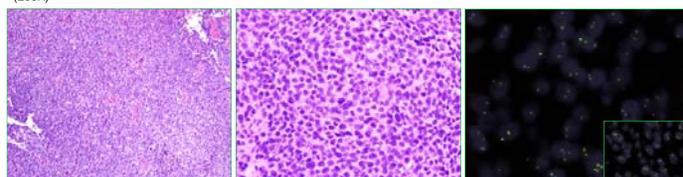
Figure 1



A case of JGCT exhibiting areas with classic morphology, comprised of primitive-appearing neoplastic granulosa cells arranged in nests and lining follicles of various sizes/shapes (200X)

Fli-1

CD99

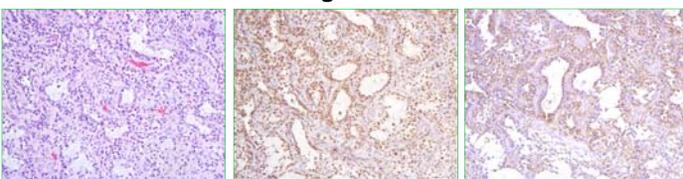


Same case, with areas of extensive sheets of tumor cells lacking follicles (100X)

The cells in these extensive sheets feature indistinct cytoplasmic boundaries, round to oval nuclei with fine chromatin and inconspicuous nucleoli – morphology characteristic of Ewing sarcoma/PNET (400X)

FISH did not demonstrate a rearrangement in *EWSR1* (1000X) (inset – positive control)

Figure 2



A case of JGCT uniformly exhibiting classic morphology (200X)

Fli-1

CD99

Results

All eleven cases of JGCT exhibited positive staining for CD99 (membranous) (Figures 1, 2). Nine cases showed diffuse staining ($\geq 75\%$ of cells); two cases exhibited focal staining (approximately 20% of cells). All eleven cases stained positive for Fli-1 (nuclear) (Figures 1, 2); staining was diffuse ($\geq 75\%$ of cells) in all cases, although the intensity of nuclear staining was variable between cases. None of the cases demonstrated a rearrangement in *EWSR1* by FISH (Figure 1).

Conclusions

- JGCTs commonly exhibit immunohistochemical expression of Fli-1; thus, Fli-1 is not a useful adjunctive marker for the distinction of JGCT from Ewing sarcoma/PNET.
- FISH testing for rearrangements in *EWSR1* can be a useful diagnostic adjunct in cases of JGCT which are morphologically and immunohistochemically indistinguishable from Ewing sarcoma/PNET.

References

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