Pediatric Sertoli-Leydig Cell Tumors of the Ovary: An Integrated Study of Clinicopathological Features, Pan-cancer-Targeted Next-generation Sequencing and Chromosomal Microarray Analysis From a Single Institution.

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要旨

卵巣 Sertoli-Leydig Cell Tumors, SLCT は稀な性索間質性腫瘍であるが、小児卵巣腫瘍の 1~2%を占める。SLCT には、*DICER1* 変異型(若年者、中/低分化型、retiform ないし heterologous elements)、*FOXL2* c.402C>G (p.Cys134Trp) 変異型(閉経後、中/低分化型, retiform/heterologous elements を有さない)、*DICER1/FOXL2* 野生型 (非若年および高齢者, retiform/heterologous elements を有さない,高分化型)という 3 種の分子 subtype が存在する。小児 SLCT の大部分は *DICER1* 生殖細胞系列変異を有する DICER1 症候群の症例で、2nd hit mutation は hotspot である RNase IIIb domain での missense 変異である。体細胞系列 *DICER1* 変異は全 SLCT の半数にみられ、小児ではほぼ全例に見られる。しかしながら小児 SLCT 集団での *DICER1* 変異以外の分子生物学的特徴については明らかになっていない。

ロサンゼルス小児病院のアーカイブ中に 8 例の小児 SLCT が確認され、それらが研究に用いられた。免疫組織化学的検討(α-inhibin, Calretinin, AE1/AE3, EMA, β-HCG, WT-1, CD99, CD10, CK7, desmin, myogenin, Melan-A)、小児悪性腫瘍に対する包括的な CGP である OncoKids、OncoScan を用いた CNA 解析、末血を用いた *DICER1* の Sanger Sequencing が行われた。

年齢の中央値は 14 歳、全例が片側発生で左右分布は均等、腫瘍径中央値は 19.8 cm、5 例が腹痛を主訴とし、うち 2 例は腫瘍破裂による緊急手術が受けていた。6 例にアンドロゲン症候(無月経 6 例、多毛 5 例、声の低音化 2 例、ざ瘡 1 例)がみられ、血清テストステロンを受けていた 7 例中 3 例で有意な上昇がみられた。7 例が中分化型、1 例は低分化型で、2 例に retiform element、1 例に heterologous elements がみられた (Table 1, Fig. 1-3.)。免疫組織化学的には、α-inhibin (8/8), calretinin (5/5), AE/1AE3 (5/5; focal), melan A (3/3)であった(Table 2)。全例に *DICER1* 変異 (RNase IIIb domain)を認め、5 例は *DICER1* の生殖細胞系列変異を有していた。残りの 3 例は複数の変異が確認された。3 例にコピー数異常を認めた(Table 3)。

Take Home Message

抄読者　刑部光正

抄読会　令和 6 年 5 月 17 日

1. 小児卵巣 SLCT は *DICER1* 変異型 SLCT であるため、補助診断として *DICER1* hot spot 変異の検出が有用である。
2. 一部の小児卵巣 SLCT は *DICER1* 以外の分子異常も有している。

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TABLE 1. Clinicopathological Features of All Sertoli-Leydig Cell Tumors

Case	Age (Y)	Symptoms and signs	TD ng/dL (<7-75)	Site	Size (cm)	Differentiated (mitotic figures)	Stage (pTNM)	Follow-up (M), treatment and other lesions
1	14	Abd mass, AC, AM, H	856↑	RO	22.0	Moderately (1MF/ 10HPF)	pT1aNxMx	112; NED; Multinodular goiter (FNA) and hepatic nodular regenerative hyperplasia (liver nodules needle core biopsy)
2	13	Abd mass	11	LO	17.5	Moderately (2MF/ 10HPF)	pT1aNxMx	77; NED; Cervical and vaginal ERMS (VAC chemotherapy), goiter, papillary thyroid carcinoma (total thyroidectomy), nasal polyps, and cystic lung lesions
3	4	Acute and severe Abd pain, Abd mass	No test	RO	12.4	Moderately (1MF/ 10HPF)	pT1c2NxMx (Ruptured and ovarian surface involvement)	70; NED
4	16	Abd pain, Abd mass, AM, H	180↑	LO	33.0	Moderately (1MF/ 10HPF)	pT1aN0Mx right iliac lymph node (0/1)	67; NED
5	14	Abd mass, AM, DV, H	47	RO	24.0	Poorly (47MF/ 10HPF)	pT1aNxMx	32; AWD; Synchronous bilateral pulmonary metastatic tumors by thoracoscopic resection biopsy revealed rhabdomyosarcomatous differentiation 1 mo after operation; Chemotherapy (15 cycles of VAC); Whole lung irradiation
6	12	Acute and severe Abd pain, Abd mass, AM	<7	LO	9.6	Moderately (2MF/ 10HPF)	pT1c2NxMx (ruptured and ovarian surface involvement)	11; NED; Chemotherapy (4 cycles of BEP)
7	16	Abd pain, AM, H	58	RO	15.0	Moderately (2MF/ 10HPF)	pT1aNxMx	10; NED
8	14	Abd pain, Abd mass, AM, DV, H	193↑	LO	25.0	Moderately (11MF/ 10HPF)	pT1aNxMx	3; NED

'↑'represents a significant elevation in serum testosterone evaluation for some patients before the operation.
Abd indicates abdominal; AC, acne; AM, amenorrhea; AWD, alive with disease; BEP, bleomycin, etoposide, cisplatin; DV, deepening voice; ERMS, embryonal rhabdomyosarcoma; FNA, fine needle aspiration; H, hirsutism; HPF, high-power fields; LO, left ovary; M, month; MF, mitotic figures; NED, no evidence of disease; RO, right ovary; TD, testosterone detection; VAC, vincristine, actinomycin, cyclophosphamide; Y, year.

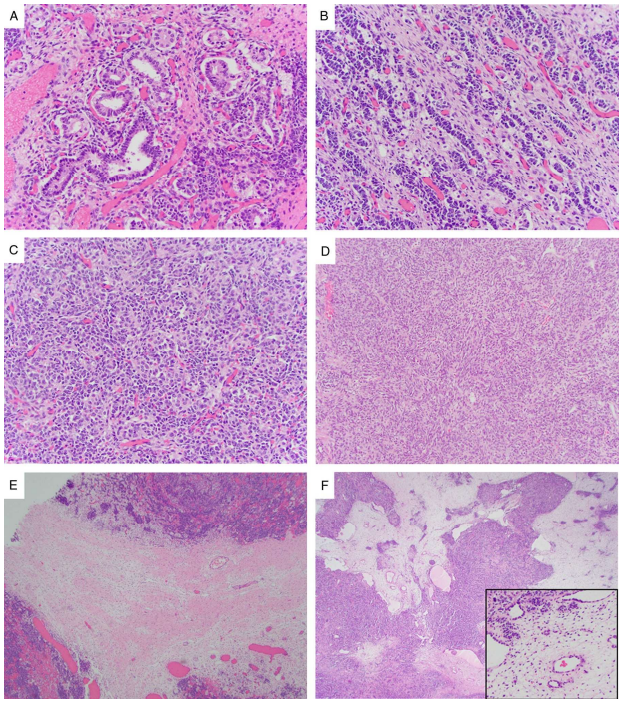

Fig. 1. The moderately or poorly differentiated SLCTs had hypercellular Sertoli cell lobules arranged in compressed tubules (A), cords/ribbons (B), diffuse sheets (C) or storiform sarcomatoid stroma resembling primitive gonadal stromal cells (poorly differentiated) (D) intersected by slightly edematous hypocellular fibromatous spindle (E) or stellate cells (F) (inset).

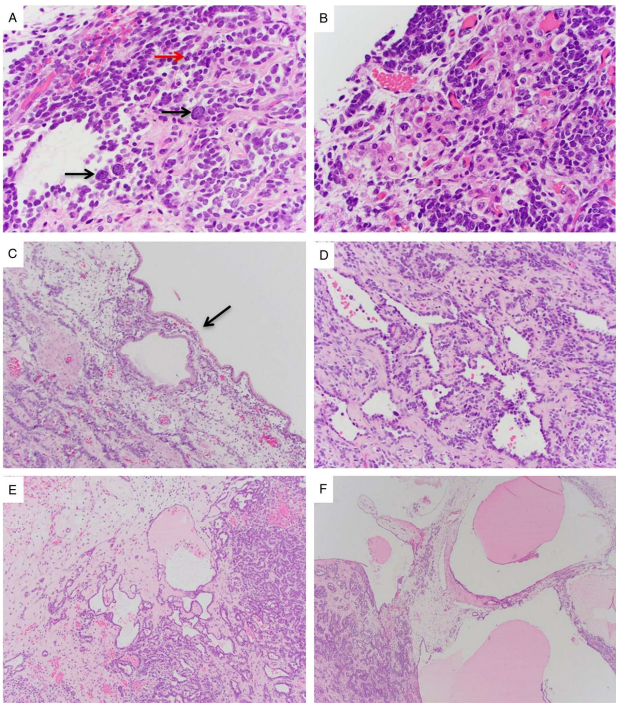

Fig. 2. Sertoli cells showed hyperchromatic, oval, or spindled nuclei with mild to moderate atypia (black arrow) and occasional mitotic figures (red arrow) (A), and Leydig cells were sparse and typically located at the periphery of tumor (B); case 1 had heterologous elements with some glands and cysts lined by bland intestinal and gastric-type epithelium (arrow) (C); some areas of case 2 showed a retiform architecture as well as cystic structures, and irregularly shaped tubules with papillae projecting into their lumens (D); case 5 had some retiform pattern with some microcysts, which are lined by hobnail cells (E) and larger dilated cysts contained eosinophilic secretion resemblance to thyroid follicles (F).

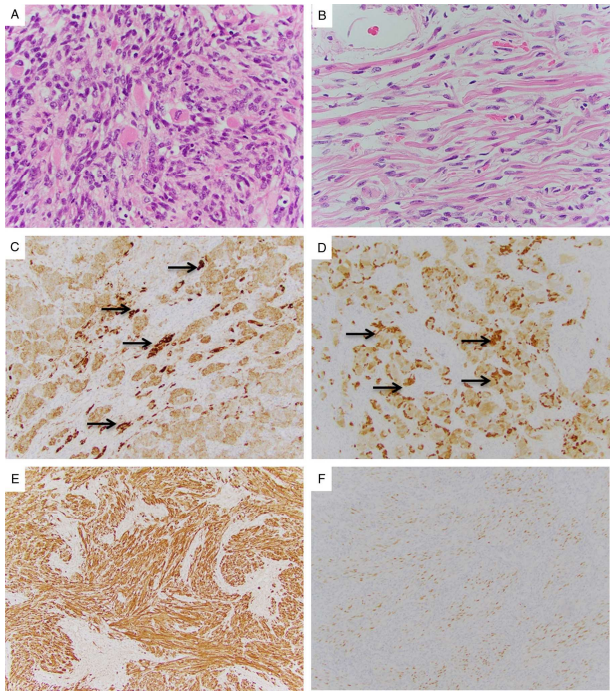

Fig. 3. Case 5 showed focal areas with rhabdomyosarcoma-like differentiation such as rhabdomyoblasts (A) and strap cells with cross-striations (B); SLCTs exhibited Sertoli cells (diffuse 2+) and Leydig cells (diffuse 3+) (arrow) for α-inhibin (C) and Calretinin (D); case 5 exhibited diffuse 3+ for desmin (E) and focal 3+ for myogenin (F) in heterologous mesenchymal elements.

TABLE 2. Results of Immunohistochemical Examination in All Sertoli-Leydig Cell Tumors

Case	α-inhibin	Calretinin	AE1/AE3	EMA	β-HCG	WT-1	CD99	CD10	CK7	Desmin	Myogenin	Melan-A
1	SC diffuse 2+, LC diffuse 3+	SC diffuse 2+, LC diffuse 3+	Focal 2+	Negative	Negative	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2	SC diffuse 2+, LC diffuse 3+	N/A	N/A	N/A	N/A	Diffuse 2+	N/A	N/A	N/A	N/A	N/A	N/A
3	SC diffuse 2+, LC diffuse 3+	SC diffuse 2+, LC diffuse 3+	Focal 2+	Negative	N/A	N/A	Negative	Focal 2+	N/A	N/A	N/A	N/A
4	SC diffuse 2+, LC diffuse 3+	SC diffuse 2+, LC diffuse 3+	N/A	N/A	N/A	Diffuse 2+	N/A	N/A	HG diffuse 3 +	N/A	N/A	N/A
5	SC diffuse 2+, LC diffuse 3+	SC diffuse 2+, LC diffuse 3+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	HME diffuse 3+	HME focal 3+	N/A
6	SC diffuse 2+, LC diffuse 3+	SC diffuse 2+, LC diffuse 3+	Focal 2+	N/A	N/A	N/A	Diffuse 3+	N/A	N/A	N/A	N/A	LC diffuse 3 +
7	SC diffuse 2+, LC diffuse 3+	N/A	Focal 2+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	LC diffuse3 +
8	SC diffuse 2+, LC diffuse 3+	N/A	Focal 2+	N/A	N/A	Diffuse 2+	N/A	N/A	N/A	N/A	N/A	LC diffuse3 +

HG indicates heterologous gland; HME, heterologous mesenchymal elements; LC, Leydig cells; N/A, not applicable; SC, Sertoli cells.

TABLE 3. Results of Molecular Examination in All Sertoli-Leydig Cell Tumors

Case	Germline *DICER1* mutation	Somatic *DICER1*/*Others* mutation/aberration
1	c.3300dupA (p.Ser1101Ilefs*3)	*DICER1*: c.5438A > G (p.Glu1813Gly)
2	c.5504_5507delATCC (p.Tyr1835Serfs*2)	*DICER1*: c.5439G > T (p.Glu1813Asp)
3	c.2436+1G > A (p.? in intron 17)	*DICER1*: c.5439G > T (p.Glu1813Asp)
4	Wild type	*DICER1*: c.3636delA (p.Gln1212Hisfs*27); c.5438A > G (p.Glu1813Ala)
5	Wild type	*DICER1*: c.5438A > C (p.Glu1813Ala); c.3052G > T (p.Glu1018*) Chromosomal microarray analysis: Gain of whole chromosome 6
6	c.2301delC (p.Cys768Valfs*5)	*DICER1*: c.5125G > A (p.Asp1709Asn)
7	c.3129delT (p.Pro1044Glnfs*22)	*DICER1*: c.5113G > A (p.Glu1705Lys) *CTNNB1*: c.110C > G (p.Ser37Cys) Chromosomal microarray analysis: Gains in 1q and 9q; loss in 10p
8	Wild type	*DICER1*: c.5425G > A (p.Gly1809Arg); c.2062C > T (p.Arg688*) Chromosomal microarray analysis: Gain of whole chromosome 6, 8 and 12; gain in 1p21.1, Xp11.23; loss in 5p15.33, 10q21.3, 18q11.2

TABLE 4. Literature Review: *DICER1* Mutation Analysis in Moderately or Poorly Differentiated Sertoli-Leydig Cell Tumors

References	*DICER1* mutation frequency no./total no. (%)	Median age (range) (y)	
		DICER1 Somatic mutation positive	*DICER1* Somatic mutation negative
Present study	8/8 (100)	14 (4-16)	No
de Kock et al[12]	29/29 (100)	19 (8-70)	No
Karnezis et al[3]	18/37 (48.6)	24.5 (15-62)	66 (17-90)
Kato et al[26]	6/10 (60)	22 (17-43)	67.5 (47-77)
Goulvent et al[15]	6/18 (33.3)	35 (17-66)	64.5 (22-69)
Merged studies	67/102 (65.7) 27/27 (100, age ≤ 16 y)	18 (4-70)	65 (17-90)