Markers and Immunoprofile of Tumors of Female Reproductive Organs

11

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11.4 Diagnostic Antibody Panel for Uterine Mesenchymal Tumors

Smooth muscle markers, CD10, and steroid hormone receptors.

p16		
Expression pattern: nuclear/cytoplasmic		
Main diagnostic use	Expression in other tumors	Expression in normal cells
HPV-associated oropharynx and uterine cervix squamous cell carcinoma, atypical lipomatous tumors and liposarcoma	Endometrial serous carcinoma, clear cell carcinoma, melanocytic nevi and melanoma, adenoid cystic carcinoma, malignant mesenchymal tumors	
Positive control: cervical squamous cell carcinoma		

Diagnostic Approach P16 (also known as INK4a or cyclin-dependent kinase inhibitor 2A) is a tumor suppressor protein encoded by the $p16^{INK4a}$ gene. p16 inhibits the cyclin-dependent kinases [1, 2] involved in in cell cycle regulation and progression (G1 to S). p16 plays role in the pathogenesis of different malignancies. The expression of p16 is regulated by the retinoblastoma (Rb) gene, which in turn is affected by the E7 oncogene of the HPV gene. p16 is overexpressed in HPV-associated intraepithelial dysplasia and squamous cell carcinomas of different origins including vulvar, vaginal, and cervical squamous cell carcinoma in addition to oropharynx carcinoma. In routine immunohistochemistry, p16 reveals cytoplasmic and nuclear staining pattern and the intensity of the stain correlates with grade of HPV infection and grade of associated dysplasia. p16 is also highly expressed in uterine serous carcinoma and a helpful marker that labels the cells of serous tubal intraepithelial carcinoma (STIC) [3].

p16 is also a useful marker to discriminate between atypical lipomatous tumors (well-differentiated liposarcoma) or other liposarcoma types positive for p16 and benign adipocytic tumors lacking the expression of p16 [4, 5].

PAX-8: PAX-8 is a transcriptional factor involved in the fetal development of the brain, eye, thyroid tissue, kidney, and upper urinary system as well as the Müllerian organs. PAX-8 is listed in detail in a next chapter.

Hepatocyte Nuclear Factor-1β (HNF-1β): HNF-1β is a member of the hepatocyte nuclear factor family regulating the growth and differentiation of hepatocytes and cells of the biliary system. The expression of different hepatocyte nuclear factors is not restricted to the liver but variously found in other organs including the pancreas, kidney, prostate, and female genital system [6]. HNF-1β is used in diagnostic immunohistochemistry to differentiate between different types of ovarian and endometrial carcinomas. The strong nuclear HNF-1β expression is characteristic for both endometrial and ovarian clear cell carcinomas but usually negative in reactive lesions with clear cell appearance such as clear cell metaplasia and Arias-Stella phenomenon [7]. However, we must consider that focal weak to moderate HNF-1β expression can be also found in other endometrial and ovarian carcinoma types such as endometrioid and serous carcinomas [8]. Additionally, different HNF-1β expression intensity is also found in other carcinomas of different origin including colorectal, pancreatobiliary, prostatic, and renal cell carcinomas.

Phosphatase and Tensin Homolog (PTEN): PTEN is a widely expressed enzyme in mammalian cells that catalyzes the dephosporylation of the 3` phosphate of the inositol ring, an essential reaction that causes the inhibition of the protein kinase (AKT) signaling pathway involved in the regulation of apoptosis. Mutations that inactivate the PTEN gene cause the inhibition of the apoptotic cascade increasing cell proliferation. Inactivating mutations within the PTEN are commonly seen in different human neoplasias

such as urogenital, breast, and lung carcinomas in addition to melanoma and glial tumors [9]. The immunohistochemical staining of PTEN (cytoplasmic pattern) is a simple way to detect the loss of this enzyme. The loss of PTEN expression is found in 30–50% of endometrial carcinoma and in about 25% of endometrium with atypical complex hyperplasia, which indicates that the loss of PTEN is not a specific marker of malignant transformation [10, 11]. Normal proliferative endometrium shows usually strong PTEN expression. The loss of PTEN expression is also found in a subset of ovarian endometrioid carcinoma (~20%), high-grade serous carcinoma, and clear cell carcinoma.

A fraction of high Gleason prostatic carcinoma is also associated with PTEN loss (see markers of prostatic carcinoma) [9]. PTEN mutations are found in primary glioblastoma but rare in secondary glioblastoma.

Steroid Receptors: Both estrogen and progesterone receptors were discussed in details with the markers of breast tumors. Endometrial adenocarcinoma and serous endometrial carcinoma are sex hormone-dependent tumors, and the expression of estrogen and progesterone is characteristic for both carcinoma types [12]. Myometrium is also a target tissue for steroid hormones; accordingly the majority of uterine leiomyomas and leiomyosarcomas are positive for estrogen receptors, progesterone receptors, or both. This characteristic feature can be used to differentiate between uterine and soft tissue leiomyosarcoma [13]. Squamous cell carcinoma and adenocarcinoma of uterine cervix usually lack the expression of both receptors [14].

Immunoprofile of tumors of the uterine cervix, uterine corpus, and fallopian tube				
Tumor type	+ in >90% (+)	+ in 50–90% (±)	+ in 10–50% (∓)	+ in <10% (−)
A. Tumors of the vulva and vagina				
Paget's disease of the vulva	CK7, EMA (MUC1), CEA, androgen receptors	ER	GCFP-15	CK5/6/14, CK20
Squamous cell carcinoma	*CK5, CK6,* CK18, CK19, *P16*			CK7, CK20
Bartholin gland carcinoma • Adenocarcinoma • Squamous cell carcinoma • Adenoid cystic carcinoma • Transitional cell carcinoma	See immunoprofile of similar carcinomas of other locations			
Adenocarcinoma of mammary type	See immunoprofile of breast carcinoma			
Adenocarcinoma of Skene gland type	Pan-CK, PSA			PAX-8
Clear cell carcinoma	CK7, EMA, CEA			CK20
Sebaceous carcinoma	*Adipophilin*, EMA, androgen receptors	Perilipin, CK5/14, CK8/18, CK7, CK19, CD15, p16		CK20, CEA, S100
Angiomyofibroblastoma	Desmin	ER, PgR	CD34	Actin

Immunoprofile of tumors of the uterine cervix, uterine corpus, and fallopian tube				
Cellular angiofibroma		CD34, ER, PgR	Actin	
Superficial angiomyxoma	CD34			Actin, desmin, S100
Deep aggressive angiomyxoma	Desmin, HMGA2	Actin, ER, PgR	CD34, actin, S100	Myogenin, MyoD1
Epithelioid sarcoma	See miscellaneous soft tissue tumors			
Rhabdomyosarcoma	See soft tissue rhabdomyosarcoma			
B. Tumors of the uterine cervix				
Squamous cell carcinoma of the cervix and uterus	*CK5, CK6*, CK13, CK17, CK18, CK19, *P16*	CK14		CK7, CK20, ER, PgR
Endocervical adenocarcinoma	*CK7*, CK8, CK18, CK19, *CEA*, EMA, *p16*, *PAX-8*		CK20, vimentin	*ER*, PgR, CK5/6, WT-1, PAX-2[a], GFAP
Endometrioid adenocarcinoma	*CK7*, CK8, CK18, CK19, EMA	*ER*, PgR, vimentin, GFAP	p16, CD56	CK20, CK5/6, *CEA*, CDX-2
Mesonephric adenocarcinoma	CK5/6, CK7, CK8, CK18, EMA, CD15	CD10, p16, *calretinin*, vimentin, bcl-2	Androgen receptors, PAX-8, TTF-1	ER, PgR, CK20, CEA
Adenosquamous carcinoma/ glassy cell carcinoma	CK7[b], CK5/6/14[c]			ER, PgR
Adenoid basal carcinoma	CK5/14, p63, p16			
Neuroendocrine tumors • NET(c) G1 • NET(d) G2 • NEC(e) G3 (small cell carcinoma)[i, k, l]	Pan-CK, *CD56*, NSE, PGP9.5 Proliferation index (Ki-67) in NET G1: <2% NET G2: 3–20% NEC G3: >20%	*Synaptophysin, chromogranin*	TTF-1	CK7, CK20
C. Tumors of the uterine corpus				
Endometrial adenocarcinoma	*CK7*, CK8, CK18, CK19, *PAX-8*, EMA, CA125	PgR, *ER*, vimentin, GFAP	CD56, p53, P16	CK20, CK5/6, CEA, WT-1, IMP3, CDX-2[d]
Serous endometrial carcinoma	CK7, CK8, CK18, CK19, EMA, CA125, *p16, p53, PAX-8*, β catenin Proliferation index (Ki-67): >75%	*IMP3*, PgR, ER	ER, PgR, Sox-2, WT-1	CK5/6, CK20, HNF1-β
Clear cell carcinoma	CK 7, EMA, CA125, *PAX-8, hepatocyte nuclear factor 1-β (HNF1-β)*, p504s (AMACR)	Vimentin, CD15	ER, AFP, CEA, p16, p53, Sox-2	PgR, WT-1, CK20, CD10
Undifferentiated carcinoma	EMA, vimentin	Pan-Cytokeratin, CK8/18, p53	PAX-8, synaptophysin, chromogranin	ER, PgR
Low-grade endometrial stromal sarcoma	*CD10*, β-catenin, vimentin	ERα, PgR, bcl-2, WT-1, TLE-1	Cyclin D1, androgen receptors, actin, desmin, pan-CK	*h-Caldesmon, calponin*, CD34, EMA, inhibin, oxytocin receptor

Immunoprofile of tumors of the uterine cervix, uterine corpus, and fallopian tube				
High-grade endometrial stromal sarcoma	Cyclin D1	CD117		CD10, ER, PgR
Uterine leiomyoma/ leiomyosarcoma	Desmin, *actin, calponin*, oxytocin receptor, p16[e], p53[e], vimentin Proliferation index (Ki-67) in uterine leiomyoma: <5% Proliferation index (Ki-67) in atypical uterine smooth muscle tumors: 5–10% Proliferation index (Ki-67) in uterine leiomyosarcoma: >15%	*h-Caldesmon*, ER, PgR	Pan-CK	CD10, EMA
Perivascular epithelioid tumor of the uterus (PEComa)	*HMB45, Melan A*, tyrosinase, MITF[f], CD63 (NK1-C3)		Actin, desmin	CD10, CD34, pan-CK, S100
Placental site trophoblastic tumor	*Human placental lactogen*, CD146, inhibin, pan-CK Proliferation index (Ki-67): >10%[g]		ßhcG	
Gestational choriocarcinoma	See choriocarcinoma of the ovary			
D. Tumors of the fallopian tube				
Serous tubal intraepithelial carcinoma (STIC)[h]	*p53*, p16, stathmin 1[i] Ki-67 > 15%			
Serous carcinoma	CK7, CK8, CK18, CK19, EMA, WT-1, *p53*, p16	ER, PgR		CK5/6, CK20
Endometrioid adenocarcinoma	*CK7*, CK8, CK18, CK19, EMA, *ER*	PgR, GFAP, vimentin	p53, CD56	P16, CK20, CK5/6, CEA, CDX-2
Undifferentiated carcinoma	EMA, vimentin	Pan-cytokeratin, CK8/18	Synaptophysin, chromogranin	ER, PgR
E. Tumors of uterine ligaments				
Epithelial tumors of Müllerian type	See uterine tumors			

[a]PAX-2 is usually expressed in benign proliferating endocervical glands
[b]CK7 positive in glandular components
[c]CK5/6/14 positive in squamous components
[d]CDX-2 may be positive in mucinous-type endometrioid adenocarcinoma
[e]P16 and p53 usually positive only in leiomyosarcoma
[f]Microphthalmia transcription factor
[g]Proliferation index (Ki-67) in placental site nodule and exaggerated placental site <1% and >50% in choriocarcinoma
[h]See Fig. 11.1
[i]Diffuse expression in STIC lesions but few scattered cells in normal fallopian mucosa [3]
[j]Well-differentiated neuroendocrine tumor (carcinoid)
[k]Well-differentiated neuroendocrine tumor (atypical carcinoid)
[l]Poorly differentiated neuroendocrine carcinoma

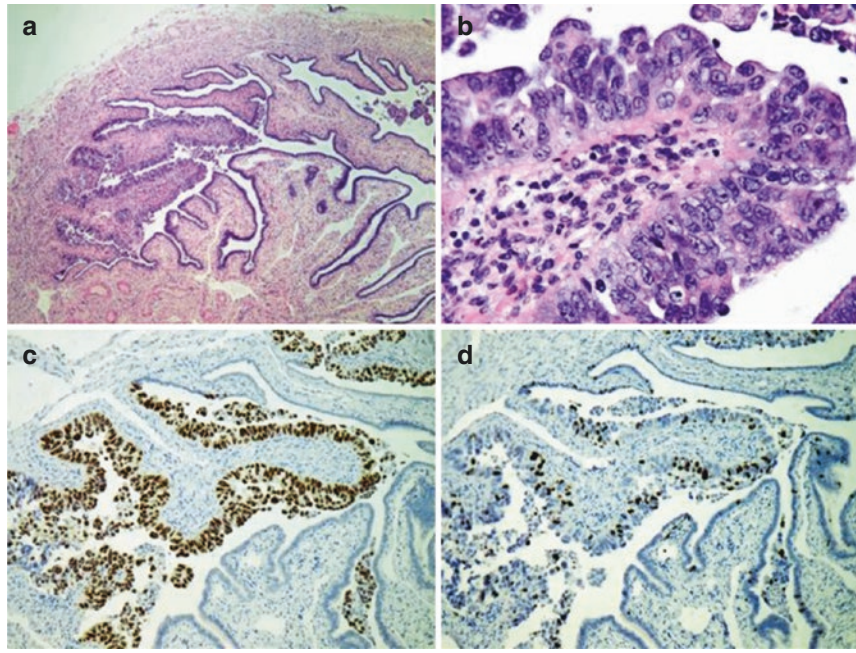

Fig. 11.1 Serous tubal intraepithelial carcinoma (STIC). (**a**, **b**) H&E 40X and 200X showing the fallopian tube with marked atypia of tubal epithelium, (**c**) same section with strong diffuse nuclear p53 expression, (**d**) Ki-67 expression in ~15% of epithelial cells

11.5 Tumors of the Ovary

11.5.1 Diagnostic Antibody Panel for Ovarian Epithelial Tumors

Cytokeratin profile, CEA, CA125, PAX-8, WT-1, p53, p16, GATA-3, S100P, steroid hormone receptors, and HNF-1β.

11.5.2 Diagnostic Antibody Panel for Ovarian Germ Cell Tumors

CD117, PLAP, Oct-4, SALL-4, Sox-2, AFP, CD30, βhcG, and cytokeratin profile (see also testicular germ cell tumors).

11.5.3 Diagnostic Antibody Panel for Ovarian Sex Cord-Stromal Tumors

Inhibin, anti-Müllerian hormone, FOXL-2, Melan A, CD56, CD99 (see also testicular sex cord-stroma tumors).

Wilms' tumor protein-1 (WT-1)		
Expression pattern: nuclear		
Main diagnostic use	Expression in other tumors	Expression in normal cells
Nephroblastoma, mesothelioma, malignant melanoma, metanephric adenoma, ovarian serous carcinoma, carcinoma of the fallopian tube	Acute myeloid leukemia, Burkitt lymphoma and subset of ALL, desmoplastic small round cell tumor, endometrial stromal sarcoma, uterine leiomyosarcoma, sex cord-stromal tumors (granulosa cell tumor, fibroma, fibrothecoma, Sertoli cell tumor), Brenner tumor, ovarian small cell carcinoma of hypercalcemic type, neuroblastoma, rhabdoid tumor, rhabdomyosarcoma	Renal tissue (glomerular podocytes), mesothelial cells, granulosa cells, Sertoli cells, fallopian tube, endometrial stroma, spleen, breast tissue, bone marrow stem cells
Positive control: appendix		

Diagnostic Approach Wilms' tumor protein-1 (WT-1) is a transcriptional regulator encoded by the WT-1 gene on chromosome 11p13 with four isoforms. WT-1 plays an important role in the regulation of growth factors and development of tissues from the inner layer of intermediate mesoderm including the genitourinary system, mesothelial cells, and spleen. Mutation within the WT-1 gene affecting the DNA-binding domain can cause the development of nephroblastoma. In routine immunohistochemistry, WT-1 shows two different expression patterns: first, a true nuclear expression pattern characteristic for different tumors such as serous carcinomas of ovarian, tubal, and peritoneal origin and mesothelioma (Fig. 11.2); secondly a cytoplasmic staining pattern found in endothelium and vascular tumors in addition to some carcinoma types such as pulmonary adenocarcinoma [1]. The cytoplasmic expression pattern appears to result from a cross reactivity with other epitopes unrelated to the WT-1 transcription factor. Endometrioid, clear cell, transitional, and mucinous carcinomas are usually WT-1 negative or show focal weak positivity. WT-1 is a helpful marker to differentiate between WT-1 positive tumors and many other WT-1 negative tumors with similar morphology such as neuroblastoma and the PNET tumor group.

Diagnostic Pitfalls WT-1 labels a high percentage of epithelioid mesotheliomas, which to consider in the differential diagnosis between ovarian peritoneal carcinosis and primary peritoneal mesotheliomas. For differential diagnosis, other antibodies such as PAX-8, Ber-EP4, and calretinin are helpful.

CA125 (MUC-16)		
Expression pattern: membranous (luminal surface)		
Main diagnostic use	Expression in other tumors	Expression in normal cells
Ovarian carcinoma (serous, endometrioid and clear cell carcinomas)	Lung, breast, gastrointestinal, uterine, and seminal vesicle adenocarcinomas, yolk sac tumor, epithelioid mesothelioma, anaplastic large cell lymphoma, desmoplastic small round cell tumor	Breast ductal epithelium, epithelium of the lung, gastrointestinal tract, biliary system, pancreas, female genital tract and apocrine glands, mesothelial cells
Positive control: serous ovarian carcinoma		

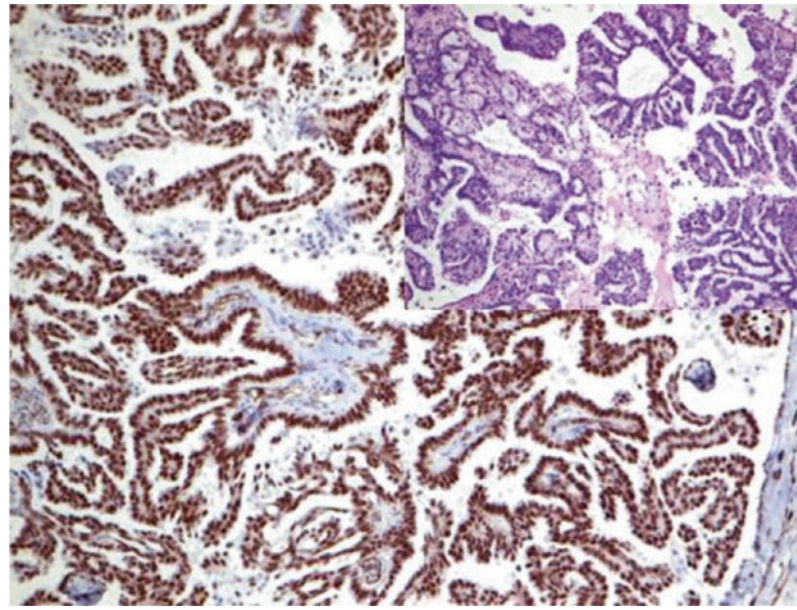

Fig. 11.2 Serous ovarian carcinoma with strong nuclear WT-1 expression

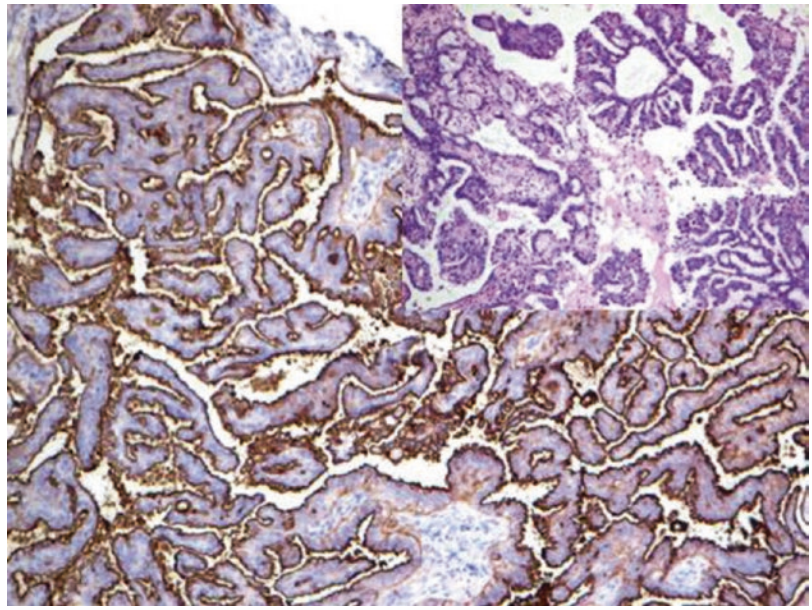

Fig. 11.3 Serous ovarian carcinoma with membranous CA125 expression

Diagnostic Approach Carbohydrate antigen 125 (CA125) is a high molecular weight glycoprotein classified as mucin 16 (MUC-16). CA125 is normally expressed by glandular epithelium of different organs and is highly expressed in ovarian serous and clear cell carcinomas (Fig. 11.3). Serum CA125 is also used to monitor the progression of ovarian carcinoma.

Diagnostic Pitfall CA125 is expressed by different epithelial and non-epithelial malignancies and lacks the specificity to ovarian carcinoma. Mesotheliomas can also be positive to CA125.

PAX-8: PAX-8 is a transcriptional factor and a member of the paired box (PAX) family listed in detail with the markers of renal cell tumors. PAX-8 is highly expressed in Müllerian glandular epithelia as well as in renal tubules and upper urinary system. PAX-8 strongly labels all uterine, endocervical, and ovarian tumors of Müllerian origin including serous, clear cell, and endometrioid carcinomas.

Hepatocyte Nuclear Factor-1β (HNF-1β): See the previous chapter (Chap. 10).

FOXL2		
Expression pattern: nuclear		
Main diagnostic use	Expression in other tumors	Expression in normal cells
Sex cord-stromal tumors	Breast cancer, pituitary gland adenoma	Granulosa cells, subset of pituitary cells
Positive control: ovarian tissue (granulosa cells)		

Diagnostic Approach FOXL2 (**f**orkhead b**ox** transcription factor **L2**) is a transcriptional factor involved in the development of the ovaries and female genital tract. FOXL2 is highly expressed in testicular and ovarian sex cord-stromal tumors including adult and juvenile granulosa cell tumors, thecoma/fibroma, Sertoli/Leydig cell tumors and sclerosing stromal tumor. Subset of pituitary gland adenomas is also positive for FOXL2, namely, gonadotropins producing adenomas and majority of null cell adenomas [2, 15, 16]. Ovarian surface epithelial tumors and germ cell tumor are FOXL2 negative.

Immunoprofile of ovarian tumors				
Tumor type	+ in >90% (+)	+ in 50–90% (±)	+ in 10–50% (∓)	+ in <10% (−)
A. Ovarian epithelial tumors				
Serous ovarian neoplasms • Adenoma • Borderline • Low-grade carcinoma • High-grade carcinoma	CK7, CK8, CK18, CK19, EMA, CA125, *WT-1, PAX-8, p53*[a], *p16*[a], HAM56 Median proliferation index (Ki-67) in serous carcinoma: Low grade ~ 2,5% High grade ~ 22%	CK5/6, mesothelin	Vimentin, ER, PgR, calretinin, S100, TTF-1, CD99	Villin, CK20, *CEA*, MUC-2, CDX-2, inhibin
Mucinous ovarian neoplasms (adenoma, borderline, and carcinoma)	CK7, CK8, CK18, CK19, EMA	CK20[b], CDX-2[b], MUC-2, MUC5AC, *CEA*, PAX-8, p53[c]	Villin	*WT-1, p16*, ER, PgR, CK17, vimentin, inhibin, TTF-1
Endometrioid carcinoma	CK7, CK8, CK18, CK19, EMA, *PAX-8*, ER, CA125	Vimentin, mesothelin, CD99	WT-1, p16, CK5	CK20, *WT-1*, CEA, inhibin, TTF-1
Clear cell adenocarcinoma	*Hepatocyte nuclear factor 1-β (HNF1-β), PAX-8*, CK7, EMA	Vimentin, CD15, CA125	AFP, CEA, napsin A, p53	*WT-1, p16, ER*, PgR, CK20, CD10
Brenner tumor (benign/malignant)	*Epithelial components*: EMA, *CK7*, p63, CEA, *CK5/6/14*[d], CA125, *Uroplakin III* *Fibrous stroma*: vimentin	*WT-1*, S100P, PAX-8 bcl-2		CK19, CK20, thrombomodulin (CD141), vimentin Pan-CK
B. Sex cord-stromal tumors				
Granulosa cell tumor	*FOXL2, adrenal 4 binding protein (SF-1), inhibin*, vimentin	Calretinin, *CD99*, actin, S100, CD56, *WT-1*, ERβ, PgR	Pan-CK, CK8, CK18, ERγ	CK7, EMA, CEA, anti-Müllerian hormone, desmin
Thecoma/Fibroma	*Inhibin, FOXL2, adrenal 4 binding protein (SF-1), WT-1*, calretinin, vimentin	sm-actin	ER, PgR	Pan-CK
Sclerosing stromal tumor	sm-Actin, PgR, *FOXL2*, vimentin	*Inhibin*, calretinin, desmin	ER	Pan-CK
Leydig cell tumor	*Inhibin*, Melan A, calretinin, vimentin	CD99, CD56	Pan-CK, S100, actin, desmin, synaptophysin, chromogranin, EMA	PLAP, AFP, CEA
Sertoli cell tumor	*Inhibin, adrenal 4 binding protein (SF-1), FOXL2, anti-Müllerian hormone*, WT-1, Melan A, vimentin	AFP, CD56, CD99, pan-CK, calretinin, NSE, S100	Synaptophysin, chromogranin	EMA, PLAP, CEA
Sex cord tumor with annular tubules	*Inhibin, adrenal 4 binding protein (SF-1)*, WT-1, calretinin	CD56	Pan-CK	EMA

Immunoprofile of ovarian tumors				
C. Germ cell tumors				
Dysgerminoma	*SAL4, Oct-4, NANOG, PLAP, CD117*	Pan-CK, D2-40	CK8/18	AFP, ßhcG, Sox-2, inhibin, S100, EMA
Embryonal carcinoma	*SALL-4, NANOG, Sox-2, PLAP, AFP, CD30, Oct-4*, pan-CK	CK19, NSE		ßhcG, *EMA*, CEA, CD117, vimentin
Yolk sac tumor	*AFP, SALL-4,* pan-CK, CD10, glypican-3	PLAP	CDX2, HepPar1	*EMA*, CD30, ßhcG, Oct-4, *Sox-2*, CK7, vimentin
Choriocarcinoma	*Syncytiotrophoblastic cells*: *ßhcG*, inhibin, CD10, pan-CK, CK8/18, CK19, GATA-3, EGFR *Cytotrophoblastic cells*: CD10, pan-CK, CK8/18, CK19, CEA	*PLAP,* human placental lactogen, EMA, CEA PLAP	Vimentin	CD30, AFP, Oct-4 ßhcG, inhibin, EMA, CD30, AFP, Oct-4
Polyembryoma	*In embryonal bodies*: *AFP*, pan-CK	PLAP		
Gonadoblastoma	*Germ cells*: PLAP, CD117, Oct-4, NANOG, D2-40 *Sex cord cells*: inhibin, WT-1, vimentin	Pan-CK		
D. Miscellaneous tumors				
Female adnexal tumor of probable Wolffian origin (ovarian Wolffian tumor)	Pan-CK, CK7, *androgen receptors*, vimentin	Calretinin, CD10, Melan A	Inhibin	EMA, CK5/6, CK20, CEA
Small cell carcinoma, hypercalcemic type	EMA, *WT-1*	Calretinin, CD56	Synaptophysin, chromogranin	CD10, inhibin
Small cell carcinoma, pulmonary type	NSE, *CD56*	TTF-1	Synaptophysin, chromogranin	

[a]High expression level characteristic for high-grade serous carcinoma, low expression level or negative in low-grade carcinoma
[b]CDX-2 and CK20 positive in mucinous adenocarcinoma and intestinal type adenoma
[c]Usually negative in adenoma and borderline tumors
[d]CK5/6/14 positive in basal epithelial cells

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