Role of immunohistochemistry in gynec oncopathology including specific diagnostic scenarios with associated treatment implications

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ABSTRACT
Over the years, immunohistochemistry has emerged as a powerful tool for a more precise diagnosis of certain tumors in gynecologic oncopathology and resolving certain diagnostic dilemmas with significant treatment implications. Certain specific immunohistochemical (IHC) markers have been useful in the more correct identification of rare tumors, characterized by specific molecular signatures. Immunohistochemistry has also been useful in the identification of underlying genetic events, characterizing various tumors, as well as precancerous lesions. This review will focus upon the judicious application of various IHC antibody markers in gynec oncopathology, including authors’ experience during “sign-outs” and especially during interaction with other oncology colleagues within the institutional disease management group. The updated references were retrieved from PubMed.

KEY WORDS: Diagnostic dilemmas in gynec pathology, gynec oncopathology, immunohistochemistry

INTRODUCTION
Invariably several tumors involving the female genital tract are diagnosed by time-honored morphological analysis, using the classic hematoxylin and eosin-stained microsections. Over the years, there has been an upsurge in the utilization of various immunohistochemical (IHC) markers in gynecologic oncopathology, especially in resolving certain diagnostic dilemmas, associated with significant treatment implications. This review will focus upon the judicious application of certain IHC makers in various clinicopathological scenarios of gynecologic oncopathology, including ovarian cancers, endometrial cancers, cervical lesions, and gestational trophoblastic tumors, especially those influencing significant treatment decisions.

Ovarian cancers
Foremost, it is a differentiation of primary ovarian versus metastatic adenocarcinoma, especially from sites such as colorectum, in cases where in tumors are identified in both, ovary and colorectum and exact diagnosis is necessary for deciding upon a specific chemotherapy regimen (fluorouracil-based chemotherapy for colorectal primary vs cisplatin-based chemotherapy for ovarian primary). The recommended IHC panel in such a scenario would include cytokeratin (CK) 7, CK20, CDX2, carcinoembryonic antigen (CEA), estrogen receptor (ER)/progesterone receptor (PR), and PAX8 (a marker of Müllerian differentiation). CK7 negative (−)/CK20 positive (+), CEA+, CDX2+ are indicative of colorectal primary (mostly left-sided tumors are CK20+/CK7−). On the other hand, CK7+, CK20−, PAX8+, CA125+ (membranous), and ER/PR+ are indicative of an ovarian primary [Figure 1].[1-3] The diagnosis of metastatic adenocarcinomas from pancreaticobiliary tract can be possibly reinforced with CA19.9 (although not very specific) and from the breast by utilizing gross cystic disease fluid protein (GCDFP), mammaglobin, and GATA3, the latter especially in triple-negative carcinomas that lack the expression of specific markers of mammary origin. GATA3, GCDFP, and mammaglobin are expressed in breast carcinomas, whereas Wilm’s tumor (WT) 1 is expressed by ovarian serous carcinomas.[4] It is noteworthy that GATA3 is a useful marker of an ovarian primary [Figure 1].[1-3] The diagnosis of metastatic adenocarcinomas from pancreaticobiliary tract can be possibly reinforced with CA19.9 (although not very specific) and from the breast by utilizing gross cystic disease fluid protein (GCDFP), mammaglobin, and GATA3, the latter especially in triple-negative carcinomas that lack the expression of specific markers of mammary origin. GATA3, GCDFP, and mammaglobin are expressed in breast carcinomas, whereas Wilm’s tumor (WT) 1 is expressed by ovarian serous carcinomas.[4] It is noteworthy that GATA3 is a useful marker of an ovarian primary [Figure 1].[1-3] The diagnosis of metastatic adenocarcinomas from pancreaticobiliary tract can be possibly reinforced with CA19.9 (although not very specific) and from the breast by utilizing gross cystic disease fluid protein (GCDFP), mammaglobin, and GATA3, the latter especially in triple-negative carcinomas that lack the expression of specific markers of mammary origin. GATA3, GCDFP, and mammaglobin are expressed in breast carcinomas, whereas Wilm’s tumor (WT) 1 is expressed by ovarian serous carcinomas.[4] It is noteworthy that GATA3 is a useful marker
for characterizing not only breast and urothelial carcinomas but also renal tumors, germ cell tumor (GCT), mesotheliomas, and paragangliomas.\(^1\)

Diffuse WT1 and p53 immunostaining reinforce high-grade serous adenocarcinoma and adenocarcinoma in situ of the fallopian tube ("p53 signature" with high Ki-67/MIB1 co-expression) [Figure 2a-c]. It is noteworthy that diffuse and intense p53 immunoreactivity in more than 70% tumor cells or complete loss (null type) is interpreted as p53 "mutation type" expression. Focal staining indicates its "wild type" expression.\(^6\) Mucinous neoplasms, including carcinomas of the ovary, are mostly considered as extra ovarian in terms of their origin. CK20+, CK7-, CDX2+, CEA+ would indicate colorectal primary, whereas CK7+, CK20+, CEA+, and p16INK4+ would indicate endocervical differentiation. The recommended panel is CK7, CK20, CEA, CDX2, and PAX8. Mucinous carcinomas are invariably not chemosensitive.\(^1\)-\(^3\)

In cases of ascites, as a result of a suspected ovarian adenocarcinoma, tumor cells can be differentiated from mesothelial cells with the help of antibody markers, such as BerEP4, PAX8, and calretinin.\(^1\)-\(^8\) Mesothelioma can be differentiated from reactive mesothelial cells, by desmin, considering the former in most cases shows a negative expression, while the latter marker shows diffuse positive immunoexpression. Epithelial membrane antigen (EMA) is another marker that can be utilized to resolve this diagnostic dilemma.\(^9\) The recommended panel is BerEP4 or MOC31, PAX8, calretinin, and desmin. Whereas an advanced high-grade serous carcinoma of the ovary is treated by cisplatin-based chemotherapy, mesothelioma is treated with surgical debulking, followed by intraabdominal chemotherapy.\(^10\)

Among primary ovarian tumors, the most frequent, high-grade serous carcinomas are invariably immunoreactive for WT1.\(^11\) At the same time, mesothelial cells display WT1 immunexpression. This is important especially when one is evaluating effusion samples. Clear cell carcinomas (CCCs) are consistently positive for Napsin A and hepatocyte nuclear factor-1β (HNF-1β).\(^11\),\(^12\) It is significant to differentiate both tumors, considering CCC ovary is relatively not sensitive to chemotherapy, in contrast to an HGSC and an endometrioid adenocarcinoma [Figures 2d-f and 3]. Endometrioid carcinomas are consistently positive for ER and PR. Serous carcinomas are also variably immunoreactive to ER and PR, unlike CCCs.\(^10\),\(^11\) Uncommonly, malignant mixed müllerian tumors (MMMTs) can be identified in the ovary, similar to the uterine counterparts, wherein epithelial and mesenchymal markers can be applied for reinforcing carcinomatous and sarcomatous components, respectively [Figure 4]. Cases with advanced tumor stage, suboptimal cytoreduction, and predominant sarcomatous component are likely to behave more aggressively.\(^14\)

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**Figure 1:** Case of serous adenocarcinoma ovary metastasizing to the rectum (a and b). (a) Unremarkable rectal mucosa (upper left) with deposits of serous adenocarcinoma (right) (H and E, ×200). (b) Higher magnification: papillary serous adenocarcinoma (H and E, ×400). Immunohistochemical (IHC) results (c-f). (c) Tumor cells showing CK7 positivity, sparing rectal mucosa (upper left) (diaminobenzidine, ×200). (d) CK20 negativity in the tumor, positivity in rectal mucosa (diaminobenzidine, ×200). (e) WT1 positivity within the tumor (diaminobenzidine, ×200) (f). CA125 positivity (diaminobenzidine, ×200)
An ovarian sex cord-stromal tumor expresses markers, such as inhibin and calretinin. OCT4 is a sensitive and specific marker for GCTs. A combination of CD30 and CKIT/CD117 is useful in differentiating an embryonal carcinoma from a dysgerminoma. OCT4 and CD30 immunoreexpression in cases of embryonal carcinoma are useful in differentiating it from a surface epithelial carcinoma. Glypican 3 is a useful marker for yolk sac tumors. It is essential to differentiate a malignant GCT from ovarian carcinoma, in view of different chemotherapy regimens for either tumor. A GCT is relatively highly chemosensitive. CCC of the ovary can be a diagnostic mimic of a yolk sac tumor, and rarely, a metastatic renal cell carcinoma. Whereas a metastatic renal cell carcinoma is immunoreactive to CD10 and PAX8, a yolk sac tumor is immunopositive to glypican 3.

Uncommonly, a round cell tumor is identified in an ovary. A recommended panel of IHC markers in such cases should include EMA, pan-cytokeratin (AE1/AE3), WT1, MIC2/CD99, inhibin, and calretinin. A small cell carcinoma ovary expresses synaptophysin, chromogranin, and thyroid transcription factor (TTF1). A small cell carcinoma ovary is positive for epithelial markers, CD10, WT1, INI1, calretinin, and vimentin, while negative for inhibin, S100P, TTF1, and inhibin. It is also associated with hypercalcemia, treated on the lines of an ovarian carcinoma, combined with etoposide and an aggressive clinical course, especially in tumors with a “rhabdoid” phenotype. MIC2, Fli1, and further molecular testing (EWSR1 rearrangement or EWS-FLI1 testing) would help in identifying rare cases of ovarian Ewing sarcoma, which is similarly treated with chemotherapy of Ewing sarcoma, at skeletal sites, but associated with an aggressive clinical course.

Figure 2: High-grade serous adenocarcinoma. (a) Markedly pleomorphic cells with interspersed frequent mitotic figures (H and E, ×400). IHC results (b and c). (b) Diffuse p53 immunostaining (mutation type), (diaminobenzidine, ×400). (c) Diffuse WT1 positivity, (diaminobenzidine, ×400). (d) Metastatic clear cell carcinoma in the lymph node in a patient treated initially as high-grade serous carcinoma, elsewhere (H and E, ×100). (e) Tumor cells showing “hob nailing,” vacuolated cytoplasm and eosinophilic bodies (H and E, ×200) (f) Napsin A positivity (diaminobenzidine, ×200), WT1 was negative.

Figure 3: Case of pelvic mass, initially diagnosed as a low-grade adenocarcinoma, elsewhere. (a) Tumor cells arranged in a solid pattern, exhibiting marked atypia and interspersed mitotic figures (H and E, ×200). (b) WT1 positivity (DAB, ×400). (c) PA × 8 positivity (DAB, ×400). (d) Complete absence of p53 immunostaining (null mutation type). (e) High Ki67/MIB1 immunostaining further reinforcing high-grade serous adenocarcinoma (DAB, ×400).
clinical course.\textsuperscript{[22,23]} Leukocyte common antigen (LCA) CD20 and myeloid peroxidase (MPO) would help in identifying a hematolymphoid neoplasm involving the ovary, associated with significant patient triaging (for bone marrow and lymph node assessment) management and therapeutic implications.\textsuperscript{[24,25]}

\section*{Endometrial cancers}

An endometrioid carcinoma (ER+, vimentin+) can be differentiated from an endocervical-type carcinoma (CEA+, p16INK4+2) using four IHC markers such as ER, vimentin, CEA, and p16INK4A in many cases \cite{Figure 7}.\textsuperscript{[26,27]} However, this is not an absolute way of differentiating both the tumors. It is imperative to know tumor epicenter (cervical or endometria) in situations of endometrial versus endocervical tumors.

Uterine serous carcinomas are treated more aggressively than endometrioid adenocarcinomas, in view of their relatively aggressive clinical behavior, including more propensity for recurrences and extrauterine spread. These tumors invariably show diffuse p53 immunostaining (mutation type) and diffuse p16INK4A immunostaining, in contrast to endometrioid carcinomas that show a relatively higher level of ER and PR immunoexpression, along with vimentin and \(\beta\)-catenin (nuclear) immunostaining, coupled with the loss of PTEN.\textsuperscript{[28-30]} Unlike ovarian serous carcinomas, uterine serous carcinomas much less frequently or rather rarely express WT1.\textsuperscript{[31]} High level of microsatellite instability as a result of mismatch repair defects (MMR-D) is observed in nearly 20\% endometrial cancers, including sporadic and those associated with Lynch syndrome. MMR-D can be immunohistochemically identified by paired loss of expression of MLH1, PMS2 or MSH2, and MSH6.\textsuperscript{[32]} Certain endometrial carcinomas showing MMR defects are associated with uncommon clinical presentations and a relatively aggressive clinical course.\textsuperscript{[33]} MMMTs are included in the category of carcinomas and treated similar to carcinomas. At times, these tumors show divergent

Figure 4: A 61 year-old-lady with adnexal tumor; malignant mixed müllerian tumor (MMMT) with heterologous elements (a and b). (a) Cellular tumor with areas of necrosis (H and E, \(\times 100\)). (b) Areas of glandular differentiation (H and E, \(\times 200\)). Inset: rhabdomyoblastic de-differentiation (H and E, \(\times 400\)). IHC results (c-e). (c) Pan cytokeratin (AE1/AE3) highlighting carcinomatous component (diaminobenzidine, \(\times 400\)). (d) Desmin highlighting rhabdomyoblastic cells (diaminobenzidine, \(\times 400\)). (e) Myogenin positivity, reinforcing rhabdomyoblastic de-differentiation (diaminobenzidine, \(\times 400\)).

Figure 5: (a) Adult granulosa cell tumor with call exner bodies and intranuclear grooves (H and E, \(\times 200\)). (b) Calretinin (nuclear and cytoplasmic) positivity (diaminobenzidine, \(\times 400\)). (c) Focal inhibin positivity (diaminobenzidine, \(\times 400\)). (d) Steroid cell tumor of the ovary, including cells showing granular to vacuolated/frothy cytoplasm (H and E, \(\times 200\)). (e) Calretinin positivity (diaminobenzidine, \(\times 400\)). (f) Focal inhibin positivity (diaminobenzidine, \(\times 400\))
differentiation (heterologous elements), such as rhabdomyoblastic, osteo and chondrosarcomatous components, with relatively more aggressive clinical outcomes, especially tumors harboring high-grade, serous, and CCC components [Figure 8].

A uterine endometrial stromal neoplasm can be differentiated from smooth muscle by CD10, SMA, desmin, and h-caldesmon, the latter three are mostly diffusely positive in smooth muscle neoplasms. An endometrial stromal sarcoma (ESS) (low-grade) invariably expresses CD10 and PR, diffusely [Figure 9a-d]. Lately, certain ESS lacking CD10 immunoperoxidase but showing diffuse cyclin D1 positivity (high-grade) have been identified [Figure 9e-h]. ESSs can show sex cord differentiation that can be reinforced by calretinin and inhibin immunostaining [Figure 10]. Lately, certain uterine mesenchymal tumors resembling sex cord tumors (UTROSCT) have been described. The lack of an index of suspicion and awareness of this entity can lead to a mistaken diagnosis of adenocarcinoma, which constitutes their differential diagnosis. Despite their overlapping IHC profile with ovarian sex cord tumors, lack of FOXL2 and DICE mutations (noted in ovarian sex cord tumors), as reported in some studies, suggests these might be genetically different from ovarian sex cord tumors.

Another mesenchymal tumor that constitutes the differential diagnosis of ESS and smooth muscle tumor is a perivascular epithelioid cell tumor (PEComa), which is composed of epithelioid and spindle cells with granular to vacuolated cytoplasm arranged around blood vessels, including nesting arrangement. The cells show melanocytic and myogenic differentiation. In the form of immunoreactivity for human melanoma black (HMB) 45, Melan A and MART-1, along with co-expression of SMA, desmin. Immunohistochemistry has been useful in uncovering certain rare tumors, such as solitary fibrous tumor (SFT), in the female genital.
tract with the help of a recently discovered immunomarker, signal transducer and activator of transcription 6 (STAT6), which is consistently expressed within this tumor, characterized by a specific gene fusion, NAB2-STAT6.\[42,43\]

A proximal-type epithelioid sarcoma, in sites, such as vulva can be mistakenly diagnosed as a carcinoma, in view of morphological features, as well as immunexpression of epithelial antibody markers, such as cytokeratin and EMA, leading to inadvertent treatment with chemotherapy. The loss of INI1 and co-expression of CD34 (in a subset of such tumors) is useful in the distinction of this tumor from a metastatic carcinoma [Figure 11].\[44,45\]

Epithelioid sarcomas, irrespective of their subtypes, are invariably treated with complete surgical excision and radiation therapy for locoregional clearance, considering these are relatively chemosensitive.\[46\] Unlike, a patient harboring a metastatic carcinoma would be a candidate for specific chemotherapy.

**Cervical lesions**

MIB1/Ki67 is useful in reinforcing the diagnosis of cervical intraepithelial neoplasia (CIN III) that shows full-thickness positive staining. The diffuse “block staining” pattern of p16INK4 is seen in a high-grade squamous intraepithelial lesion (SIL)/CIN associated with high-risk human papillomavirus (HPV) infection than its mimic, that is, atrophy [Figure 12].\[47\]

While most endocervical adenocarcinomas display p16INK4A and CEA immunostaining, certain unusual patterns of cervical adenocarcinoma include clear cell, gastric-type, minimal deviation, serous, MMMT, and mesonephric types.\[48\] A neuroendocrine carcinoma of cervix (NECC) can be differentiated from a poorly differentiated (PD) or basaloid squamous cell carcinoma (SCC), especially on a limited biopsy by CD56/neural cell adhesion molecule (NCAM), synaptophysin, and chromogranin that are variably positive in the NECC, while

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**Figure 8:** MMMT of the endometrium. (a) Malignant tumor with glandular architecture (H and E, ×200). (b) Areas of sarcomatous differentiation (H and E, ×200). (c) Distinct rhabdomyoblastic cells (heterologous differentiation) (H and E, ×400). (d) Desmin highlighting rhabdomyoblasts (diaminobenzidine, ×400)

**Figure 9:** Low-grade ESS (a-b). (a) Tumor composed of short spindly cells with interspersed blood vessels (H and E, ×200). (b) Periarteriolar arrangements (H and E, ×400). IHC results (c-d). (c) Diffuse CD10 immunopositivity (diaminobenzidine, ×200) (d) PR positivity (diaminobenzidine, ×400). High-grade ESS (e-f). (e) Spindle cells with intercellular collagen (H and E, ×200). (f) Diffuse cyclinD1 positivity (CD10, focal) (diaminobenzidine, ×200). (g) Recurrence (H and E, ×400). Inset: YWHAE rearrangement (red-green split signals) (DAP1, ×1000) (h) Cyclin D1 positive recurrent ESS (diaminobenzidine, ×400)
Figure 10: ESS with sex cord differentiation (a and b). (a) Tumor showing features of ESS H and E, ×200. (b) Intervening tubular structures, reminiscent of sex cord differentiation including in the inset (H and E, ×400). IHC results (c–g). (c) Diffuse CD10 immunopositivity (diaminobenzidine, ×400). (d) PR positivity (diaminobenzidine, ×400). (e) MIC2 highlighting interspersed sex cord elements (diaminobenzidine, ×400). (f) Calretinin highlighting sex cord elements (diaminobenzidine, ×400). (g) Focal, distinct inhibin positivity (diaminobenzidine, ×400)

Figure 11: Vulvar tumor. Epithelioid sarcoma, proximal-type. (a) Cut surface of vulvectomy specimen displaying gray-white tumor in the dermis. (b) Microscopy: tumor composed of cells with polygonal shapes, prominent nucleoli and moderate to abundant eosinophilic cytoplasm, forming “rhabdoid-like” inclusions (H and E, ×200). (c) CK positivity (diaminobenzidine, ×400). (d) Diffuse CD34 positivity (cytoplasmic membranous) (diaminobenzidine, ×400). (e) Tumor cells displaying loss of INI1. Interspersed nuclei and endothelial cells showing intranuclear staining (control) (diaminobenzidine, ×400)
p63 and p40 are more diffusely expressed by PDSCC. Rare case scenarios of metastatic tumors can be resolved by the application of certain tumor-specific markers [Figures 13 and 14]. NEC Cs of the cervix also display p16INK4 immunopositivity.⁴⁹

Melanomas, although rare in the vulvovaginal sites, are mimics of carcinomas, sarcomas, and lymphomas. The optimal panel of IHC markers for identification of melanomas includes S100 protein, HMB45, and Melan A with SOX10 a new marker of melanocytic and neural differentiation [Figures 15].⁵⁰⁻⁵² Application of IHC markers, such as leukocyte common antigen (LCA), along with lineage specific markers, namely CD3 and CD20 are helpful.
in accurately diagnosing specific types of non-Hodgkin’s lymphomas [Figure 16]. Diagnosis of a high-grade Non-Hodgkin’s lymphoma of B cell type would lead to subjecting the patient to a specific chemotherapy regimen, unlike other tumors, including carcinomas and sarcomas.

**Gestational trophoblastic tumors**

Within the realm of gestational trophoblastic tumors, p57 is useful in the diagnosis and molecular triage of molar specimens, such as differentiating complete hydatidiform moles from partial moles and non-molar specimens. In an earlier study, McConnell et al.\(^5\) identified diffuse p57 immunostaining in 4/7 partial moles and in all 17 non-molar specimens; while the same was absent in 23/24 cases of complete moles, including seven cases of early complete hydatidiform mole.

P63, human placental lactogen, and ki67 are useful in separating out trophoblastic lesions. p63 immunostaining is associated with the chorionic trophoblastic disease, whereas HPL, secreted by syncytiotrophoblasts, is highly expressed in the trophoblasts of placental site trophoblastic tumors (PTT) and exaggerated placental site reaction (EPS), but minimally expressed in epithelioid trophoblastic tumors (ETT) and placental site nodules (PSN). In PSTTs and ETT, 8–20% of cells stain positive for Ki-67, whereas, in EPS, the intermediate trophoblasts stain negatively for Ki-67. Beta-human chorionic gonadotropin (B-hCG) is used to identify choriocarcinoma that also shows high Ki-67.\(^5\) In early-stage disease, choriocarcinomas are treated with chemotherapy, in contrast to trophoblastic tumors that are treated with surgical removal/hysterectomy. High-grade carcinomas that are mimics of these tumors might be chosen for aggressive chemotherapy regimes.

It is noteworthy that immunostaining results of tumors involving the female genital tract, similar to tumors occurring at other
sites should be interpreted with clinicopathologic features and. Morphology guides toward ordering a correct, optimal panel of IHC markers for a particular case that would have further therapeutic implications.

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There are no conflicts of interest.

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