Immunohistochemistry of Gynecologic Malignancies

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Abstract

Since its first discovery in 1930, immunohistochemistry (IHC) became a staple in all pathology departments. Its usage gained popularity in early 1970 when "immunoperoxidase" method to formalin paraffin-embedded tissues was developed. In recent days, this ancillary technology becomes a routine and essential tool in diagnostic and research laboratories. Application of IHC in medical practice is commonly used in helping to identify the origin of malignancy, predicting prognosis, and helping select targeted therapy. Gynecologic pathology is not an exception. Example and just to name a few, pair box gene 8 (PAX8) has been used to identify the Müllerian origin of a carcinoma, alpha-inhibin and calretinin for sex cord tumor. In this chapter, we will describe the principle and the interpretation of IHC, and we will discuss various immunomarkers that are commonly used in gynecologic pathology.

Keywords

Immunohistochemistry • Principles • Gynecologic malignancies • Differential diagnosis • Prognostic diagnosis

Contents

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1 Introduction

Immunohistochemistry (IHC) refers to the process of detecting antigens (e.g., proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues. These antibodies can be cytoplasmic or nuclear or they can shuttle between the cytoplasm and the nucleus. In recent days IHC has become a routine and essential tool in diagnostic and research laboratories. In this chapter we will discuss the principle, interpretation, pitfalls, and role of the most common immunomarkers in gynecologic pathology.

2 Basic Principle of Immunohistochemistry

Modern immunohistochemistry (IHC) uses an indirect method, so-called "sandwich" method. It consists of three parts, (1) specific antibodies, (2) bridging compound, and (3) detection system that are described below:

1. Specific antibodies, also called primary antibodies, are commonly IgG and less frequently IgM. Specific antibodies react with antigens of interest, and they can be polyclonal or monoclonal antibodies. Polyclonal antibodies are collected from the antisera of immunized animals by antigen(s) of interest. The antisera is then purified and become commercially available for clinical use. They react with multiple epitopes of the same antigen, making them highly sensitive but less specific.

   Monoclonal antibodies are a population of homogeneous immunoglobulin reacting specifically with a single epitope. A monoclonal antibody is manufactured from a so-called hybridoma, a fused and immortalized cell line; a myeloma cell line/fusion partner fused with immunized B-lymphocytes isolated from animal spleen. B-lymphocytes confer the capability to produce specific immunoglobulin, while the fused partner cell line enables immortality and indefinite growth in culture. The advantage of monoclonal antibody comparing to polyclonal antibody is that it is very specific and very consistent.
2. Bridging compound, commonly called "secondary antibody," is a biotinylated nonspecific anti-antibody reacting with primary antibodies. It functions as a link between the primary antibody and detecting systems.
3. The detecting system witnessed significant changes since immunohistochemistry was first introduced. The immunoperoxidase bridging method and the peroxidase antiperoxidase (PAP) complex method were used earlier; however, the avidin-biotin is now the dominant method. It consists mainly of the avidin-biotin complex (ABC or BAC). Avidin or streptavidin has strong affinity for biotin with four biotin-binding sites. The biotin molecule is easily conjugated to second antibody and enzyme (peroxidase) then forming the avidin-biotin-peroxidase complex which catalyzes chemical reaction of substrate and chromogens.

2.1 Interpretation of Immunohistochemistry

Immunoreactivity of cells of interest can be nuclear, cytoplasmic, cell membranous, or a mixture of any of these patterns. Positivity of immunostains is defined by specific pattern of immunoreactivity of cells of interest. For example, S100 and TTF1 can be cytoplasmic, but they are considered positive when they exhibit only nuclear immunoreactivity. In general, immunostains can be interpreted for intensity and percentage as well as diffuse, focal, or rare expression. As for intensity, the result of an immunostain is reported as negative or as positive with weak, moderate, or strong intensity. On

the other hand, the percentage of positive cells is arbitrary and somewhat subjective.

Immunostains can have false positive and false negative. Causes of false positive can be positive cells that are not the cells of interest, wrong staining pattern (e.g., cytoplasmic instead nuclear), intrinsic peroxidase (commonly seen in inflammatory cells), background staining, and edge effect. Causes of false negative can be loss of cells of interest on deeper cut, bad fixation, loss of antigen during tissue process, and technical problem. To get correct interpretation, it is essential that the pathologist is familiar with tumor morphology and staining interpretation and has good external and internal control. Therefore, experience in surgical pathology and deep knowledge of IHC can avoid these pitfalls.

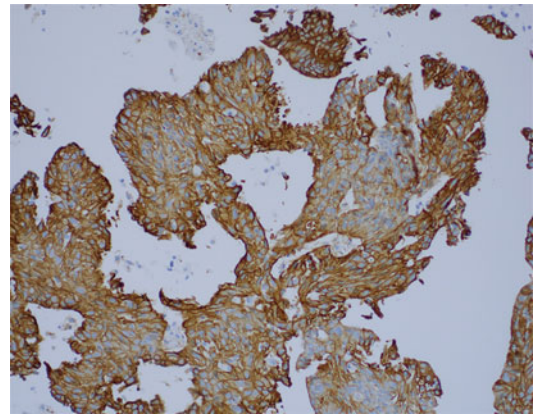

Fig. 1 Total cytokeratin (AE1/3) is positive in a cytoplasmic pattern, indicating that this malignancy is a carcinoma

3 Common IHC Markers Used in Gynecologic Malignancies

3.1 Epithelial Markers

3.1.1 Cytokeratin

Cytokeratin (CK) or simply called keratin is a group of intracytoplasmic proteins of keratin-containing intermediate filaments found in all type of epithelial tissue. It is a common epithelial marker and generally functioning as cytoskeleton. There are 20 common subtypes of keratins. All epithelial cells will express one or more subtypes of keratins. There are two types of keratins: type 1 (acidic) comprising CK 9, 10, 12, and 14–20 and type 2 (basic) comprising CK 1–8. Type 1 and type 2 cytokeratins are in pairs. Cytokeratins can also be divided into low and high molecular weight (LMW and HMW) based solely on their molecular weight. In general, type 1 keratins are low molecular weight keratins, and type 2 keratins are high molecular weight keratins. AE1/AE3 is a cocktail of anti-keratin antibodies. AE1 mainly includes CK10, 11, 13, 14, 15, 16, and 19 and AE3 contains CK1, 2, 3, 4, 5, 6, 7, and 8. It can be slightly variable from manufacture to another. In gynecologic pathology, AE1/AE3 has a cytoplasmic pattern, and it is used to identify cells of epithelial origin, like carcinomas (Fig. 1). However, it also can be positive in some non-epithelial cells like epithelioid leiomyosarcoma and perivascular epithelioid cell neoplasm (PECOMA). The unique CK7 and CK20 expression by carcinomas has been proven to be useful to recognize the origin of these epithelial tumors, and they are regularly used in the IHC workup of malignancies of unknown origin. Tumors of the gynecologic tract are usually CK7+/CK20-, but exception occurs as ovarian mucinous adenocarcinomas can be CK7+/CK20+ (Chu et al. 2000).

3.1.2 Epithelial Membrane Antigen (EMA)

EMA is another epithelial marker. It is a membrane bound, glycosylated phosphoprotein, the product of the MUC-1 gene (1). It is often expressed in the cytoplasm of nearly all epithelial cells. Therefore it can be used as an alternative or subsidiary to other epithelial marker. However it can also be positive in some non-epithelial tumors, such as sarcoma, namely, synovial sarcoma.

3.1.3 Pair Box Gene 8 (PAX8)

It is a member of paired-box (PAX) family of transcription factors. It is involved in embryogenesis of the thyroid, Müllerian, and renal/upper urinary tracts as a nephric-lineage transcription factor. PAX8 is a nuclear stain that is highly sensitive and site-specific marker for thyroid, Müllerian, renal, and thymic neoplasms (Ozcan et al. 2011). In gynecologic pathology, it has been

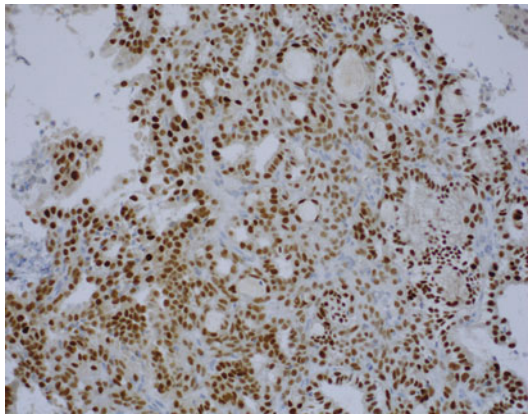

Fig. 2 PAX8 is positive in a nuclear pattern. PAX8 positivity in a tumor of unknown origin indicates that the tumor is of probable gynecologic tract origin

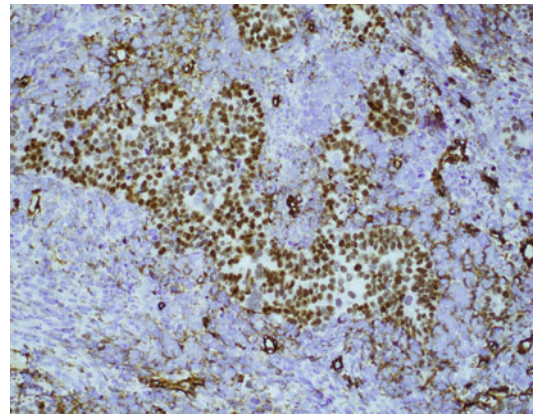

Fig. 3 WT1 is positive in nuclear pattern in a metastatic serous ovarian carcinoma to the vulva

widely used in identifying tumor of Müllerian origin, including most of ovarian epithelial neoplasms, endometrial carcinomas, and cervical adenocarcinoma (Fig. 2). It is usually negative in cervical squamous cell carcinoma and mesenchymal tumors of the female genital tract.

3.1.4 Wilm's Tumor 1 (WT1)

It is a marker traditionally used to diagnose Wilms' tumor. Wilms tumor protein is a transcription factor encoded by the WT1 gene on human chromosome 11p and serves an essential role in the normal development of the urogenital system. This gene is mutated in a subset of patients with Wilms' tumor. WT1 immunostain gains its popularity in gynecology-pathology due to its nuclear positivity in the vast majority of serous carcinoma of ovary (Fig. 3). Another use of WT1 is to help differentiating endometrial serous carcinoma versus ovarian serous carcinoma, as it is negative in the former and positive in the latter. Because WT1 is frequently positive in mesothelial cells, caution is needed when evaluating malignant cells in peritoneal cytology (Moritani et al. 2008).

3.2 Mesenchymal Markers

3.2.1 Vimentin

It is a type 3 intermediate filament protein that is expressed in mesenchymal cells and the major cytoskeletal component of mesenchymal cells. Therefore, vimentin is often used as a marker of mesenchymally derived cells or cells undergoing an epithelial-to-mesenchymal transition (EMT) during both normal development and metastatic progression. It has a cytoplasmic pattern of expression. In gynecologic pathology it can be positive in endometrial glandular cells and its tumor derivatives. This characteristic feature is very helpful in distinguish adenocarcinoma originating from the endometrium versus the endocervix.

3.2.2 Actin

Actins are microfilaments existing essentially in all eukaryotic cells. They are expressed in many cellular processes, including muscle contraction, cell motility, cell division and cytokinesis, vesicle and organelle movement, cell signaling, and the establishment and maintenance of cell junctions and cell shape. Actins include both alpha-smooth muscle actin (SMA) and muscle-specific actin (MSA) that are equally expressed in skeletal muscle, smooth muscle, myofibroblasts, myoepithelial cells, and pericytes in a cytoplasmic pattern.

3.2.3 Desmin

Desmin is an intermediate filament in skeletal, cardiac, and smooth muscle. Desmin immunostain has a cytoplasmic pattern of expression, and it is useful to identify neoplasms of skeletal, cardiac, and smooth muscle origin, but not for myoepithelial cells, and less than actin for myofibroblasts.

3.2.4 Myoglobulin, MyoD1, and Myogenin

These are skeletal muscle-specific markers often used in identifying rhabdomyosarcoma and rhabdomyosarcomatous component in carcinosarcoma. Myoglobulin is present in well-differentiated skeletal muscle cells.

3.2.5 Transgelin

Transgelin is an actin-binding protein of the calponin family that correlates with smooth muscle differentiation. It is a good marker for smooth muscle differentiation, and recently it proved to be a good marker to differentiate leiomyosarcoma from endometrial stromal sarcoma, where it is positive in the former and negative in the latter.

3.3 Sex Cord Markers

3.3.1 Alpha-Inhibin

Alpha-inhibin is a subunit of an inhibitor of pituitary FSH secretion, encoded by the INHA human gene. Inhibin also participates in the negative regulation of gonadal stromal cell proliferation and has tumor suppressor activity. Alpha-inhibin has a cytoplasmic pattern, and it is widely accepted as a marker for sex cord tumor as it is positive in the vast majority of sex cord stromal tumors such as granulosa cell tumor, Sertoli cell tumor, or a Sertoli cell in Sertoli-Leydig cell tumor. When alpha-inhibin is combined with calretinin (another marker for sex cord stroma tumor), the sensitivity as well as the specificity is highly increased (Deavers et al. 2003; Jones et al. 2010).

3.3.2 CD30

CD30 is also known as ki-1. It is a member of the tumor necrosis family of cell surface receptors and is a lymphocytic activation antigen. It is mostly expressed in classic Hodgkin's lymphoma, large cell anaplastic lymphoma, and embryonal carcinoma of the testis and the ovary.

3.4 Trophoblastic Markers

3.4.1 Human Chorionic Gonadotropin (hCG)

hCG is a polypeptide hormone with two subunits: α- and β-subunits. Naturally, it is produced in the human placenta by the syncytiotrophoblast. β-subunit (β-hCG)-specific immunostain will highlight normal syncytiotrophoblasts, choriocarcinoma, hydatidiform mole, and syncytial trophoblastic cells in tumors containing syncytial trophoblastic cells.

3.4.2 Human Placental Lactogen (hPL)

hPL is another polypeptide hormone produced by syncytial and intermediate trophoblasts. The intensity of immunostain is stronger on intermediate trophoblastic cells than on syncytial trophoblastic cells. Intermediate trophoblastic cells can be positive, but they are most likely negative for hCG. hPL staining is very useful for the diagnosis of placental site trophoblastic tumor due to the predominance of proliferation of intermediate trophoblastic cells in this tumor.

3.5 Other Immunomarkers

3.5.1 Ki67/MIB 1

This marker was originally described in Kiel, Germany, where the name was originated. It is a cellular marker for cell proliferation, and it is encoded by MKI67 gene in human. Ki67 protein is a nuclear protein, and it is present in all cells during the proliferative phases (G1, S, G2, M) and is not present in cells in the resting phase. It has a nuclear staining pattern and provides a proliferation index (Ki67 index). Each given tumor has its own meaningful Ki67 index. In general, the higher Ki67 index associates with more aggressive tumor behavior and worse prognosis. In gynecologic pathology, Ki67 has been commonly used to distinguish between benign and dysplastic lesions of the cervix. It is very useful in differentiating endocervical adenocarcinoma from reactive endocervical glands and in distinguishing squamous cell atrophy from squamous dysplasia of the exocervix.

3.5.2 P53

P53 is an oncoprotein is encoded by TP53 gene that is located on chromosome 17. TP53 is called the "guardian of the genome." It is a tumor suppressor gene and is the most frequently mutated gene in human tumors. In gynecologic pathology, TP53 mutation has been associated with high-grade serous carcinoma. Positive p53 expression in approximately 60% of tumor cells or greater, or completely negative p53 expression (p53 null) are both indicative for TP53 mutation and, therefore, are considered helpful in confirming high-grade serous carcinoma. P53 immunostain has a nuclear pattern. It can be positive, such as clear cell type and high-grade endometrioid type, and mucinous type.

3.5.3 P16

P16 is a tumor suppressor protein and a surrogate marker for high-risk HPV-related neoplasia and carcinoma. A positive result is defined as diffuse, strong nuclear, and cytoplasmic expression by the cells of interest. It is very specific in differentiating squamous intraepithelial neoplasia/carcinoma of cervix from reactive changes. Because of overlapping immunoreactivity with adenocarcinoma of other origin, the use of p16 by itself to identify tumor origin is not of great use.

3.5.4 ER and PR

ER and PR are hormonal receptors seen in the entire female genital tract (Fig. 4). They are used to distinguish endocervical from endometrial cancer where they are negative in the former and positive in the latter. In addition, they are used for therapeutic options in patients with endometrioid adenocarcinoma and endometrial stromal sarcoma.

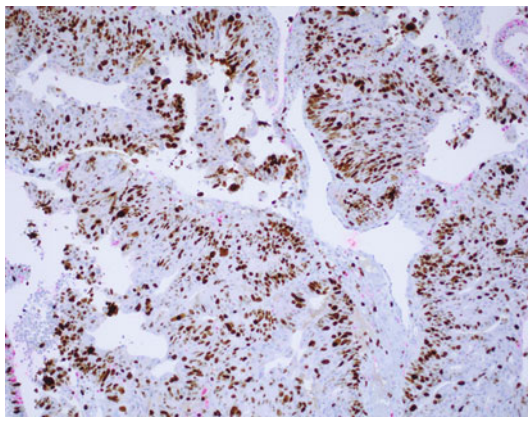

Fig. 4 ER is strongly positive in nuclear pattern in an endometrial adenocarcinoma endometrioid type, FIGO 1

3.5.5 Insulin-like Growth Factor II mRNA Binding Protein 3 (IMP3)

IMP3 plays an important role in RNA trafficking, stabilization, cell growth, and cell migration during early stages of embryogenesis. IMP3 has a cytoplasmic and an apical pattern. It is useful to differentiate endometrioid adenocarcinoma from serous carcinoma of the endometrium where it is negative in the former and positive in the latter (Zheng et al. 2008; Mhawech-Fauceglia et al. 2010, 2013).

3.5.6 CD10

CD10 also known as CALLA (common acute lymphocytic leukemia antigen). It is a hematologic marker encoded by the MME gene and is expressed by many hematopoietic malignancies. In the gynecologic tract, it is expressed by the cytoplasm of endometrial stromal cells making it very useful in the diagnosis of endometrial stromal sarcoma (ESS) and for distinguishing ESS from smooth muscle tumor. Other tumors positive for CD10 include many renal cell carcinomas such as clear cell type, solid pseudopapillary type, as well as some urothelial tumors.

4 Application of IHC to Female Genital Tract

4.1 Vulvar Lesions

The most frequent lesion of the vulva is extramammary Paget disease of the vulva and Bowen's disease. Even though melanoma does not commonly occur in the vulva, it is still included in the differential diagnosis (Table 1). It is essential to distinguish among these lesions due to their different treatments and outcomes.

Table 1 Immunohistochemistry markers helpful in differentiating among different types of vulvar lesions

		Second Paget disease			
	Primary Paget disease	Anorectal	Urothelial	Bowen	Melanoma
CK7	+ (100%)	–	+	–	–
CK20	–	+	+ (variable)	–	–
GCDFP-15	+ (88%)	– (100%)	– (100%)	–	–
CEA	+	+	–	–	–
Specific markers	**CAM 5.2**		Thrombomodulin		S100, HMB45 Melanan A
	Androgen		**Uroplakin III**		

4.2 High-Risk HPV-Related Cervical Neoplasms Versus Benign Reactive Cervical Lesions

High-risk HPV-related cervical neoplasms, squamous and adenocarcinoma, and their precursors are positive for both p16 (strong and diffuse) and Ki67. On the other hand, benign reactive lesions are negative or positive for only one marker but not for both p16 and Ki67.

4.3 Endometrial Endometrioid Adenocarcinoma Versus Endocervical Adenocarcinoma

The panel of immunohistochemistries (IHCs) such as CEA monoclonal, ER/PR, vimentin, and p16 are used to differentiate endometrial adenocarcinoma from endocervical adenocarcinoma. Endometrial adenocarcinomas are positive for vimentin, and ER/PR and endocervical adenocarcinomas are positive for CEAm and Muc1. P16 is unable to differentiate between the two as it is positive in both (Mhawech-Fauceglia et al. 2008; Reid-Nicholson et al. 2006).

4.4 Serous Carcinoma, Endometrial Versus Ovarian Origin

WT1 is very useful to differentiate ovarian serous adenocarcinoma (90% positive) from endometrial serous carcinoma (90% negative). WT1 is also useful to distinguish among histologic ovarian subtypes as we will be discussing in the next paragraph (Acs et al. 2004).

4.5 Ovarian Carcinomas Histologic Subtypes

There is no single reliable immunomarker that can distinguish among various ovarian carcinomas histologic subtypes (Baker and Oliva 2004; Kobel et al. 2008). However, a panel of antibodies including p53, WT1, and ER might be helpful (Table 2).

4.6 Clear Cell Carcinoma of Ovary

Clear cell carcinoma (CCC) can be very difficult to diagnose, and other tumors with similar morphology should be excluded:

1. **Metastatic Renal Cell Carcinoma**: ovarian CCC is negative for vimentin and CD10; renal cell carcinoma is positive for vimentin and CD10.
2. **Dysgerminoma:** CCC is positive for AE1/AE3 and EMA; dysgerminoma is negative for AE1/AE3 and EMA.
3. **Yolk Sac Tumor:** AFP and glypican-3 are positive in yolk sac tumor and negative in CCC (McCluggage and Young 2005).

4.7 Mucinous Carcinoma of Ovary Versus Lower Gastrointestinal (GI) Tract

Ovarian mucinous carcinomas are positive for CK7 and either positive or negative for CK20 and CDX2. Mucinous carcinomas of lower GI tract are negative for CK7 and positive for CK20 and CDX2.

Table 2 Immunohistochemistry markers expressions in ovarian surface epithelial malignancies

Carcinomas	WT1 (%)	TP53 (%)	ER (%)
LGSC	100	0	96
HGSC	92	93	80
Mucinous	0	50	6
Endometrioid	4	11	86
Clear cell	0	12	13

Table 3 Immunohistochemical markers useful in discriminating among different subtypes of germ cell tumors of the ovary

	Dysgerminoma	Yolk sac tumor	Embryonal carcinoma	Choriocarcinoma
AE1/AE3	– or +weak	+	+	+
EMA	–	+	–	+
CD30	–	–	+	–
CD117	+	+	–	–
OCT-4	+	–	+	–
Glypican-3	–	+	+	+
AFP	–	+	+ in rare cells	
HCG	+ rare cells		+ in rare cells	+

4.8 Endometrioid Adenocarcinoma Versus Metastastic Adenocarcinoma from the GI Tract

Endometrioid adenocarcinomas are positive for CK7, ER/PR, and vimentin and negative for CK20 and CDX2. However, metastatic carcinomas from the GI tract are negative for CK7 (except upper GI carcinomas which they are positive for CK7), positive for CK20 and CDX2, and negative for ER/PR and vimentin.

4.9 Endometrial Stromal Sarcoma (ESS) Versus Leiomyosarcoma

ESSs are positive for CD10 and negative or sometime weakly positive for SMA, transgelin, and desmin; leiomyosarcomas are strongly positive for SMA, transgelin, and desmin, and they are negative or occasionally weakly positive for CD10. ER and PR are usually positive in ESS. These immunostains are not usually useful in high-grade ESS and leiomyosarcoma (Hwang et al. 2015).

4.10 Germ Cell Tumors

IHC is very useful and often done to differentiate among germ cell tumors including dysgerminoma, yolk sac tumor, embryonal carcinoma, and choriocarcinoma (Table 3). Making the right diagnosis is essential for patient management and outcome.

5 Conclusion

IHC is used regularly in medical practices and is commonly used in helping to identify the origin of malignancy, predicting prognosis, and helping select targeted therapy.

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