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Review Article

An update on the use of immunohistochemistry and molecular pathology in the diagnosis of pre-invasive and malignant lesions in gynecological oncology

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HIGHLIGHTS

- Identification of the type and the primary origin of a tumor is a real challenge in everyday clinical practice.
- Immunohistochemistry localizes particular antigens in a cell or tissue founded on antigen-antibody recognition.
- Immunohistochemistry is as a major diagnostic tool in gynecology, for precise tumor classification.
- Immunohistochemistry has a strong role in the development of personalised medicine in the future.
- Molecular pathology has taken disease subclassification further resulting in more effective tailored treatment regimens.

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ABSTRACT

Objective. One of the most common challenges in everyday clinical practice of gynecological oncology is to identify the type and the primary origin of a tumor. This is a crucial step in the management, treatment, prognosis, and survival of patients suffering from a gynecological malignancy. Immunohistochemistry has been widely adopted over the last three decades in pathology laboratories all over the world. Recent advances in our understanding of the differentiation of gynecological tumors based on immunohistochemical expression have resulted in use of immunohistochemistry as a major diagnostic tool in gynecology, for precise tumor classification. More recently, advances in molecular pathology, have taken this disease sub-classification further resulting in more effective personalised treatment regimens. The aim of this review is to provide clinicians with up to date information on the various immunohistochemical and molecular tests used in the diagnosis of gynecological malignancies of the female genital tract and an understanding of how to interpret them.

Methods. We performed a review of the current literature including review articles, original research articles, and guidelines on various immunohistochemical markers and molecular techniques which are used for the differential diagnosis of gynecologic malignancies.

Conclusions. Immunohistochemistry is useful as an objective means for improved diagnostic reproducibility, accuracy, and precise classification in cases where the diagnosis with histochemical stains is inconclusive, providing a more reliable estimate of clinical outcomes. The diagnosis, in some cases, can be further refined by the use of molecular techniques leading to personalised medical treatments.

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Contents

1. Introduction

One of the most common challenges in everyday clinical practice of gynecological oncology is to identify the type and the primary origin of a tumor [1–4]. This is a crucial step in the management, treatment, prognosis, and survival of patients suffering from a gynecologic malignancy [1–4].

The microscopic assessment of tissue specimens for many decades has routinely used hematoxylin and eosin (HE) histochemical stain, which has provided accurate, fast, and relatively inexpensive information regarding the diagnosis, tumor grade and pathologic stage for the majority of cases [1–4]. However, lesions with inconclusive morphologic features present a diagnostic challenge and, in recent years, the identification of specific genetic alteration has adjusted some traditional morphological diagnostic categories. To improve the diagnostic accuracy and prognostic information, pathologists may include additional tests such as histochemical stains for mucin (mucicarmine and AB-PAS), immunohistochemistry and molecular techniques [1–4].

Immunohistochemistry is a method for localizing particular antigens in a cell or tissue founded on antigen-antibody recognition to demonstrate the presence of a specific protein within the specimen under microscopic examination [1–4]. It has been widely adopted over the last three decades in pathology laboratories all over the world. Its recent expansion in the field of gynecological pathology has contributed to improved precision in tumor classification [2].

Immunohistochemistry is at its most useful, proficient and cost effective when undertaken in the knowledge of the clinical history, radiologic studies, and laboratory data [1,5]. Based on the estimated immunophenotype of the entities in the differential diagnosis, a suitable panel of antibodies may be selected [1–4]. Newly introduced markers might be more accurate in the diagnosis of certain tumor types but diagnostic assumptions based on them have to be made with caution, as data may be insufficient with an overly optimistic impression on specificity [5]. Thus, combination with the use of well-established immunohistochemical markers is often diagnostically more reliable and histological evaluation from an experienced pathologist who is aware of all diagnostic possibilities and their histological variants is mandatory even when immunohistochemistry is used [5].

This update reviews immunohistochemical and molecular markers used in gynecological oncology, including established and emerging techniques. Moreover, this review provides clinicians an understanding of how to interpret the most common used immunohistochemical markers.

Immunohistochemistry and molecular markers in the differential diagnosis of pre-invasive lesions and the most common gynecological malignancies.

2. Uterine tumors

2.1. Endometrial precursor lesions

Differing terminology has been used to describe precursor lesions of the endometrium that predispose to 80% of cases of endometrioid endometrial adenocarcinoma [6,7]. The classification of endometrial lesions into benign hyperplasia and endometrial intraepithelial neoplasia (EIN) separates the histologic features seen consequent on unopposed estrogen from those due to the accumulation of neoplastic mutations [6,7].

β-catenin mutations have been described in atypical endometrial hyperplasia [8]. Furthermore, Phosphatase and tensin homolog (PTEN) mutations have been found in endometrial hyperplasia, with or without atypia, with loss of PTEN and paired box (PAX)2 in 55% and 71% of EIN cases respectively [9]. PAX2 and PTEN protein loss was seen to occur independently, accumulating with increasing age in latent pre-cancers of normal premenopausal endometrium [10]. However, in common practice, diagnosis of precursor lesions of endometrioid endometrial carcinoma generally relies on the morphology on the HE sections [6,7].

EIN should not be confused with serous endometrial intraepithelial carcinoma (SEIC) which presents in atrophic endometrium and is the precursor lesion of uterine serous carcinoma [11]. Pure serous EIC can

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