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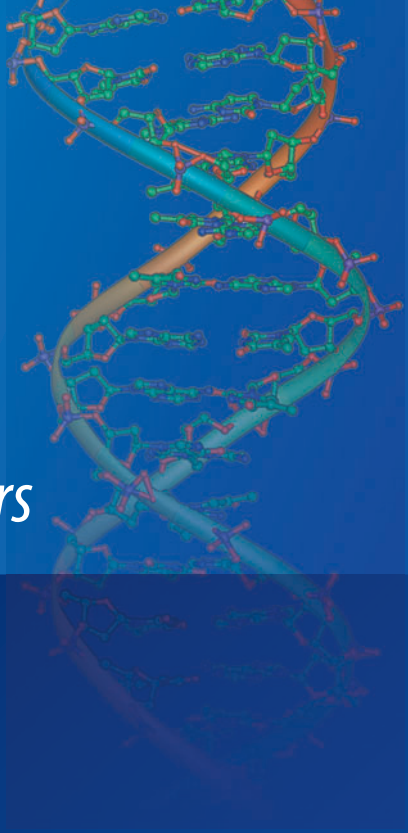

Michael T. Deavers
Donna M. Coffey *Editors*

Precision Molecular Pathology of Uterine Cancer

Springer

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Precision Molecular Pathology of Uterine Cancer

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ISSN 1935-987X ISSN 1935-9888 (electronic)
Molecular Pathology Library
ISBN 978-3-319-57983-2 ISBN 978-3-319-57985-6 (eBook)
DOI 10.1007/978-3-319-57985-6

Library of Congress Control Number: 2017943170

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Contents

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Part I
Introduction

Chapter 1
Endometrial Carcinoma: Precursor Lesions and Molecular Profiles

Sudeshna Bandyopadhyay and Rouba Ali-Fehmi

Introduction

Endometrial carcinoma is the most common gynecological malignancy. Approximately 54,870 endometrial carcinomas were diagnosed in 2015 with 10,170 deaths [1]. It has been categorized into 2 groups based on histopathology, clinical findings, and outcome and molecular findings. The biology of these tumors is underpinned by genetic and molecular features. This dichotomy in clinical, pathological, and molecular features validates a dualistic classification of endometrial carcinoma, which includes Type I and Type II cancers. Type I lesions include endometrioid carcinoma and its subtypes, while serous carcinoma is a prototype of Type II. These differences have also been identified at the precursor level, whereas uterine serous carcinomas (USCs) comprise less than 10% of all endometrial carcinomas, but paradoxically cause a high proportion of relapses and endometrial cancer-related deaths.

Endometrioid Carcinoma (Type 1)

Endometrioid carcinoma is the prototype of Type I endometrial cancer. These tumors have been linked to increased and prolonged estrogenic stimulation, occur in pre- and perimenopausal women, and occur in a background of hyperplasia [2]. Typically, they are diagnosed at a lower stage and have a good prognosis.

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M.T. Deavers and D.M. Coffey (eds.), *Precision Molecular Pathology of Uterine Cancer*, Molecular Pathology Library,
DOI 10.1007/978-3-319-57985-6_1

Precursor Lesions

Endometrioid adenocarcinoma occurs in a background of endometrial hyperplasia which is characterized morphologically by architectural complexity, cytological atypia, or both. The architectural patterns include cystic dilatation of the endometrial glands and a spectrum of more complex changes including glandular out pouching with back-to-back glandular proliferation, papillary infolding into the gland lumen with budding, villoglandular patterns, and cribriform architecture. An increase in the gland to stromal ratio of approximately 3:1 is also noted in hyperplasia [3]. Simple hyperplasia indicates an increased gland to stroma ratio, while complex hyperplasia denotes back-to-back glands with a more complex architecture. Based on the degree of architectural atypia (simple versus complex) and superimposed cytological atypia characterized by nuclear rounding and pleomorphism, vesicular chromatin with prominent nucleoli, increased N:C ratio, and loss of polarity, these lesions are classified as follows:

1. Simple hyperplasia without atypia;
2. Simple hyperplasia with atypia;
3. Complex hyperplasia without atypia;
4. Complex hyperplasia with atypia [4].

These morphological variations each have been assigned a different attributable risk of progression to carcinoma. The maximum risk of progression to endometrial carcinoma is associated with complex atypical hyperplasia, estimated to be 29%, while complex hyperplasia without atypia has an estimated risk of about 3% [5]. In another study, it was shown that the risk of progression to carcinoma in women with non-atypical endometrial hyperplasia was <5%, while almost 30% of women with atypical endometrial hyperplasia were diagnosed with endometrial carcinoma [6].

Up to 50% of women with atypical hyperplasia on the endometrial biopsy have endometrial carcinoma in the resection specimen [7–9].

The progression of hyperplasia to adenocarcinoma has common underlying molecular abnormalities detected in both these lesions. These have been described in a later section.

Uterine Serous Carcinoma (Type 2)

USC comprises less than 10% of all endometrial carcinomas, but paradoxically cause a high proportion of relapses and endometrial cancer-related deaths, which is a testimony to its biologically aggressive nature [10, 11]. Advanced stage disease (Stage III and IV) has a dismal prognosis with a 3-year survival of about 56% [12]. USC was first recognized by Lauchlan [13] and then described by Hendrickson as an endometrial carcinoma with histology similar to ovarian serous carcinoma [10]. Its defining histological features and distinctive behavior have been validated in subsequent studies [14–16].

USC usually occurs in postmenopausal women, in the milieu of an atrophic endometrium [17]. Although it was traditionally considered to be estrogen independent (as opposed to the endometrioid type), it has become increasingly evident that estrogen production continues after menopause from extra-ovarian sources, and therefore, it is fair to say that USC is more likely estrogen deficient than estrogen independent (reviewed in [18]). High-grade histological features characterize USC. These tumors exhibit severe nuclear pleomorphism, hyperchromasia, prominent nucleoli, increased mitotic activity, and single cell apoptosis, akin to ovarian serous carcinoma (Figs. 1.1 and 1.2). Additionally, the cells are dyshesive and lack cell polarity. Contrary to the high-grade cytology, these tumors tend to form glands (lined by these highly atypical cells). In addition, areas of papillary and solid architecture are also seen. Also seen are characteristic slit-like spaces and budding/micropapillae. These tumors, diagnosed later in life, often arise in a background of atrophic endometrium [10, 16, 19]. Clinically, the aggressive biology of USC has been well established, and this underlies the interest that has been generated in this disease. These tumors are biologically distinct with a poorer

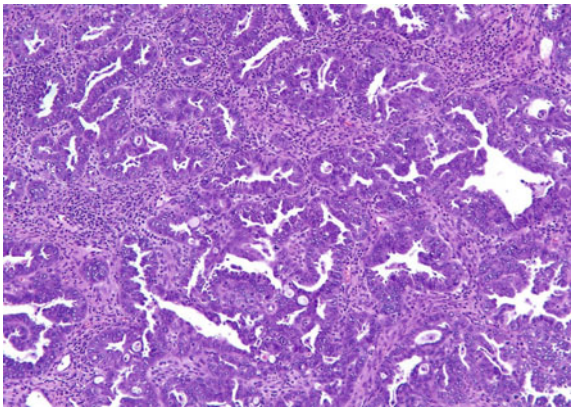

Fig. 1.1 Low power section from endometrial serous carcinoma glandular pattern

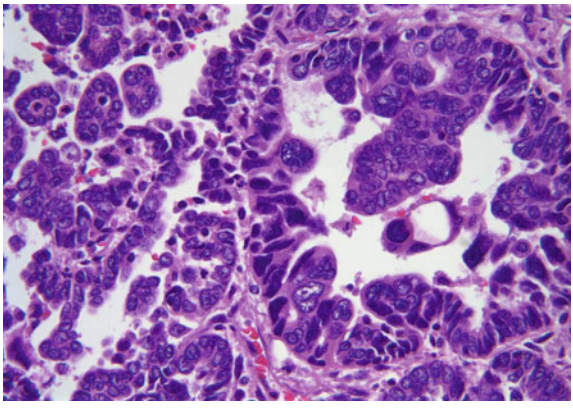

Fig. 1.2 High power illustration of endometrial serous carcinoma presenting the significant cytologic atypia and the floating papillae

prognosis compared to stage-matched endometrioid carcinomas [11, 20, 21]. Sherman et al. had argued that a diagnosis of serous carcinoma is used when at least 25% of the tumor is serous in nature [16]; however, other investigators have reported that any serous component in mixed tumors will confer a worse prognosis compared to endometrioid carcinomas [22, 23]. Also, it has been determined that the usual risk factors to predict recurrence in endometrioid carcinomas may not be useful to assess the risk of recurrence in USC [23]. At clinical presentation, these tumors are more commonly diagnosed at a high stage with evidence of extrauterine spread [24, 25]. Slomovitz and colleagues have reported a significant frequency of extrauterine disease (37%) and a poor prognosis [26] in patients with small endometrial lesions that do not invade the myometrium. Wheeler et al. [27] looked at a subset of "minimal USC" which included a cohort of EIC and superficial serous carcinoma, characterized as USC without myometrial or lymphovascular invasion. In their experience, 25% of the EIC cases and 26% of the superficial serous carcinoma cases had extrauterine disease. In another series of patients diagnosed with "minimal USC," Hui et al. [28] found extrauterine disease in 45% of the patients. In a more recent study which included a cohort of USC without myometrial invasion, Semaan et al. [29] reported that 1.8% of the cases had Stage II disease, 1.8% had Stage IIIA, and 16.4% of the cases had stage IVB disease.

The association of serous carcinoma with endometrial polyps was first described by Silva and Jenkins [30]. In their study, they described 16 patients with USC involving a polyp with minimal or no myometrial invasion. Six of these 16 (37.5%) patients also had extrauterine disease. Involvement of an endometrial polyp was also found in 30.9% of cases in series of USC limited to the endometrium, reported by Semaan et al. [29], and of these, 29.4% had stage IVB disease. Numerous studies have also identified a high risk of lymph node metastasis (ranging from 13 to 36%) in patients with uterine serous carcinoma without myometrial invasion [20, 26, 31]. These findings underline the fact that the traditional risk factors associated with endometrial carcinomas may not be applicable in USC.

Precursor Lesions

Serous endometrial intraepithelial carcinoma (EIC) also known as "endometrial carcinoma in situ," "surface serous carcinoma," and "minimal USC" is considered to be the precursor to USC, first recognized as intraepithelial carcinoma present adjacent to serous carcinoma [14, 16, 32]. This lesion is described as composed of cytologically malignant cells, similar to those seen in USC, lining the surface of the endometrium or endometrial glands without invasion of endometrial stroma, myometrium, or lymphovascular spaces [33]. It is often seen in conjunction with USC, which raises the possibility that this might be a precursor lesion. Pure EIC is a rare disease. Although technically noninvasive in appearance, these tumors have been associated with extrauterine disease, reflecting their aggressive biology [25–27, 31]. Identical p53 mutations in EIC and the pelvic serous component have been