Wenxin Zheng
Oluwole Fadare
Charles Matthew Quick
Danhua Shen
Donghui Guo
Editors

Gynecologic and Obstetric Pathology, Volume 2

Science Press
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Foreword

The field of gynecologic and obstetric pathology is at a cross-roads. In the past decade we have begun to witness the departure of venerated contributors to this discipline and now we are being inundated with new information about pathogenesis that informs diagnostic expectations and patient outcome. The old model in which the next generation sits at the knee of the learned and patiently awaits their turn at the helm is rapidly fading. Succession is now not simply achieved by learning the old language but by speaking a new one.

The textbook *Gynecologic and Obstetrics Pathology*, edited by Drs. Zheng, Fadare, and Quick is emblematic of the sea change. We've all heard the joke about resorting to one's grandchild to solve a computer conundrum. How many of us turn to our younger colleagues to interpret emerging genomic information in the management of gynecologic cancer? An appreciation of such talent is crucial to our evolution as well as that of our discipline.

The senior editor in this project, Dr. Wenxin Zheng, has a long track record of innovation. With this has come a facility to recognize the most talented young clinician-investigators and to recruit them into this new textbook. Drs. Fadare and Quick as well as the younger chapter authors are well on their way, having already put us on notice that by their dedication, creativity and their role in discovery. Their input is what will keep this and subsequent editions at the forefront of pathology texts dedicated to women's health.

Energy and intellect drive discovery but experience is essential to provide a needed perspective when this information is transmitted to the practicing pathologist. The editors wisely balance the list of talented newcomers with recognized experts in the field. Together they provide the finer details of diagnosis and differential diagnosis while eliciting the nuances relevant to clinical management.

In the current world, where discoveries and their impact on practice can become global almost instantaneously, one does not need to travel far to realize that expertise in obstetric and gynecologic pathology is intercontinental. In recognizing this, Zheng et al. will also provide an edition written in Chinese, bringing this message to pathologists (and their patients) in countries where the language is read and spoken. To my knowledge, this book will be the first of its kind to accomplish this, creating a truly international presence that will place this first edition among the leading texts in the field. The editors and authors are to be commended for their contribution and I look forward to their success in opening a new chapter (and book!) in the history of the pathology of the female reproductive tract.

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Preface

Pathology of the female genital tract is complex, and encompasses a wide spectrum of neoplastic and non-neoplastic diseases of the gonads, reproductive ducts, secondary müllerian system, and external genitalia. Clinical practitioners in this discipline must therefore familiarize themselves with a broad spectrum of pathology, including skin-like diseases of the vulva, a myriad of peritoneal diseases, as well as conventional diseases of other female genital tract organs. This field progresses in a vibrant and dynamic academic environment in which diagnostic concepts continually evolve as our understanding of various disease processes improves over time. The contemporary gynecologic pathologist is in a unique position to recognize and define morphologic correlates to newly defined genomic profiles and individual gene mutations, assess whether they are likely to have diagnostic or prognostic significance for a given patient and/or her family, and broadly participate in the push towards increasingly personalized cancer care. These exciting trends notwithstanding, it remains true that definitive pathologic classification of gynecologic disease is still primarily based on the traditional pillars of surgical pathology, including gross pathology, morphologic assessment buttressed by immunophenotypic analysis where needed, and careful clinicopathologic correlation.

This book is envisioned as a "bridge" that acknowledges both of the aforementioned realities. It is designed to provide a broad coverage of diagnostic gynecologic and obstetric pathology, inclusive of both neoplastic and non-neoplastic diseases. The book is neither a dense and comprehensive treatise on every disease process nor is it a dry listing of relevant "facts" about each entity. Rather, it is best conceptualized as a large scale aggregation of the most up to date information in gynecologic pathology, all presented in a concise and narrative manner that is designed to be easily accessible to the general practitioner, specialist and student alike. An overt effort has been made to discuss each topic in a way that is maximally relevant to the diagnostic surgical pathologist, such that by reading any section should substantially increase the reader's confidence that the most germane clinicopathologic information on that entity has been reviewed before a diagnostic decision is made.

The material is organized into 36 chapters, representing the full spectrum of diagnostic gynecologic pathology. In addition to chapters on traditional topics in gynecologic pathology, there are individual chapters on site-specific carcinogenesis, gynecologic cytology, intraoperative consultation, endometriosis and development/maldevelopment of the female reproductive system, among others. Additionally, in a departure from most current texts, there are stand-alone chapters to provide intensive coverage of some traditionally under-covered topics, including melanocytic lesions of the female genital tract, non-neoplastic diseases of the endometrium, and vulvovaginal soft tissue lesions. Entities with a significant diagnostic component are presented, where feasible, divided into the following subsections: *Clinical features, Gross findings, Microscopic findings, Differential diagnosis, Biomarkers,* and *Genetic features.* As expected, not all entities or chapters lend themselves to this specific format, but most chapters are broadly structured based on these general themes. Microscopic findings are lavishly illustrated, and numerous tables help summarize pertinent points for easy reference. The overall objective of each chapter is to integrate traditional pathologic features, clinical features, where applicable, and current paradigms in disease classification into a format that can be readily applied in routine practice. These chapters are authored by over 50 physicians, most of whom

are experienced subspecialty practitioners of clinical gynecologic pathology from around the world, and without whose expertise, dedication, and diligence this work would not have been possible. It is the sincere hope of the editors that all of those who are interested in gynecologic pathology—diagnostic pathologists, students, residents and investigators—will find this book tremendously useful.

The understanding of gynecologic disease involves pathologists and researchers from across oceans and all over the world, and to that end an exciting feature of this book is that it is written with a direct linkage to the second edition of the book "Gynecologic and Obstetric Pathology". The latter book is in Chinese, and is published by Science Press, Beijing, China. The current text is published in both English and Chinese, representing a collaborative effort by both publishers: Springer and Science Press. Although the titles and the number of chapters are identical in the two books, the authors of the chapters are different. Additionally, while the chapter outlines and some of the contents overlap, the two books do not represent a direct translation from one to the other. Rather, they are best considered complementary "sister" books. This results from Dr. Wenxin Zheng serving as the first editor-in-chief for both books. Considering this special and close relationship, the co-editors for the Chinese book, Drs. Danhua Shen and Donghui Guo, are listed as co-editors of the English version of this book, while Drs. Fadare and Quick are also listed as co-editors on the second edition of the Chinese book.

Dallas, TX — Wenxin Zheng
San Diego, CA — Oluwole Fadare
Little Rock, AR — Charles Matthew Quick

Acknowledgments

To my dear wife Wenda and my beloved family (Yuxin, Genfu, and Deshun) for their constant love and endless support! In memory of my parents Maoguan Zheng and Jinxian Wang as well as my ultimate mentor Dr. Stuart C. Lauchlan.

Wenxin Zheng

To my wife Abby for her love, encouragement, and inspiration, and to our beloved children Nathaniel, Darrell and Olivia for (mostly) putting up with the occasional absences that were required to do this.

Oluwole Fadare

To my everything, Shelly, and my wonderful children Dexter, Bernice, and Alice.

Charles Matthew Quick

To my beloved family members for their continuous support and care, and to all my colleagues who participated in editing this outstanding book. I am honored to be an editor for this prestigious book.

Danhua Shen

To my beloved family members for their constant support and care, and to Drs. Zhaoai Kong and Song Lin whose past instruction and training have been and continues to be invaluable.

Donghui Guo

The Editors would like to sincerely thank Dr. Christopher P. Crum, M.D. for serving as a senior consulting adviser for this book. Dr. Crum has made significant contributions to the field of gynecologic pathology and has trained innumerable residents and fellows, including many who have served as an author for this book. The quality of this work is in part attributable to his years of dedicated teaching and research in the field of gynecologic pathology.

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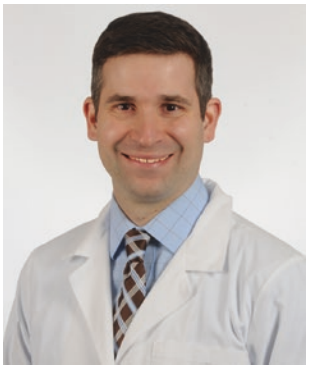
About the Editors

Oluwole Fadare Dr. Oluwole Fadare is a Professor of Pathology at the University of California San Diego School of Medicine (UCSD, San Diego, CA, USA), where he also serves as the Chief of Anatomic Pathology for the UCSD Health System and Director of the Gynecologic/Breast Pathology fellowship. Dr. Fadare completed a fellowship in breast and gynecologic pathology at the Yale University School of Medicine (New Haven, CT, USA) in 2005, and has spent his subsequent academic career focused on the pathologic aspects of women's health. Dr. Fadare has been the recipient of numerous prestigious awards, including most recently the 2018 Arthur Purdy Stout Prize from the Arthur Purdy Stout Society of Surgical Pathologists in recognition of "significant career achievements in Surgical Pathology by a Surgical Pathologist (less than 45 years old) whose publications have had a major impact on diagnostic pathology", a 2018 Stowell-Orbison Certificate of Merit from the United States and Canadian Academy of Pathologists (USCAP), and a 2017 Excellence in Mentoring Award from UCSD Health Sciences International "in recognition of a sustained commitment to helping create a cadre of global leaders in innovative academic medicine". Dr. Fadare has published more than 200 peer-reviewed articles in high impact scientific journals, predominantly centered on gynecologic pathology. Previous books edited or co-written include *Diagnosis of Neoplasia in Endometrial Biopsies: A Pattern-Based and Algorithmic Approach* (Cambridge University Press, 2014) and *Precancerous Lesions of the Gynecologic Tract: Diagnostic and Molecular Genetic Pathology* (Springer 2015). Dr. Fadare has served in various editorial capacities for over 80 journals, and is currently an editorial board member for the *International Journal of Gynecological Pathology, Human Pathology, Advances in Anatomic Pathology, Archives of Pathology and Laboratory Medicine, Archives of Medical Research*, and *Diagnostic Pathology*, among others. He is also active in various professional societies, and currently serves on the education committee for the International Society of Gynecologic Pathologists and on the membership committee for USCAP. Dr. Fadare's research has been clinical based, and has focused on integrating morphological, immunohistochemical and molecular aspects of gynecologic tract neoplasms to optimize diagnostic, prognostic and predictive patient care.

Donghui Guo Dr. Guo graduated from the Fourth Military Medical University of China in 1974, and is one of the top gynecologic pathologists in China. Mentored by Professor Song Lin in the early part of her career, Dr. Guo has practiced gynecologic pathology for more than 30 years. Dr. Guo served as Chairman in the Department of Pathology, Tianjin Central Hospital of Obstetrics and Gynecology for 10 years. She has mentored many graduate students, residents, and fellows with an interest in gynecologic pathology. Dr. Guo has served as a committee member as well as a well-recognized expert in gynecologic pathology for many professional societies in China. Dr. Guo has completed 4 major scientific achievements (please provide the details here) with multiple awards in Tianjin, China. Dr. Guo has authored and co-edited 5 pathology books and has published more than 30 peer-reviewed articles.



Charles Matthew Quick Dr. Charles "Matt"hew Quick is an associate professor and clinical educator in the Department of Pathology at UAMS in Little Rock, Arkansas. He completed fellowships in surgical pathology at UAMS and Women's & Perinatal pathology at Harvard Medical School, Brigham & Women's Hospital. Dr. Quick serves as the Director of Anatomic Pathology Sub-Specialty Practice, Gynecologic Pathology, and the Surgical Pathology Fellowship.

He has published numerous research publications and review articles, and has authored and co-edited multiple textbooks, including "High-Yield Pathology: Gynecologic and Obstetric Pathology." He loves all things teaching and gynecologic pathology related and has won numerous teaching awards for his medical student and resident education efforts, including UAMS's campus-wide "Chancellor's Award for Teaching Excellence." Dr. Quick is dedicated to expanding pathology education in medical school and has started numerous programs at UAMS to effect this change including the UAMS pathology interest group: SCOPE, a summer pathology preceptorship, and the integration of autopsy pathology into the first year gross anatomy course, earning him an Education Innovation award in 2015. His efforts have led to a dramatic increase in medical students choosing pathology as a career in the state of Arkansas.

Dr. Quick serves as an Ambassador for the United States and Canadian Academy of Pathology, and has taught numerous interactive microscopy courses for the USCAP at both annual meetings and the new teaching complex located in Palm Springs, California. He serves as the Gynecologic Pathology Course Director for the USCAP Interactive Microscopy Center. Dr. Quick's research interests include the study of endometrial precancers, vulvar squamous carcinogenesis and the impact of epithelial-mesenchymal transition on tumor behavior.

Danhua Shen Dr. Danhua Shen, Associate Professor of Pathology, is the Chairman of the Department of Pathology, People's Hospital of Peking University, China. Dr. Shen is one of the top gynecologic pathologists in China. In addition to her dedication to pathology diagnosis, Dr. Shen has participated in many research projects of *National Natural Science Foundation of China.* She is the head of the *Female Reproductive Diseases Group of the Pathology Branch of the Chinese Medical Association*, and serves as an executive committee member for many prestigious professional societies including the *Chinese Gynecologic Oncology Group, Chinese Society of Obstetrics and Gynecology*, and *Chinese Society of Colposcopy and Cervical Pathology*, etc. Dr. Shen is also an editorial board member for the *Journal of Chinese Pathology* and the *Chinese Journal of Obstetrics and Gynecology*, and the *Journal of Diagnostic Pathology*.

Dr. Shen has published more than 100 peer reviewed articles, and has been involved in seven clinical and pathological related monographs/books or book chapters either as an editor-in-chief or deputy editor-in-chief. Dr. Shen has also participated in many book translations in the field of Pathology and Obstetrics and Gynecology.

Wenxin Zheng Dr. Zheng is a tenured Professor in the Department of Pathology and the Department of Obstetrics and Gynecology at the University of Texas Southwestern Medical Center (UTSW). An internationally recognized gynecologic pathologist as well as active physician scientist, he specializes in all aspects of gynecologic pathology and holds the Mark and Jane Gibson Distinguished Professorship in Cancer Research. Dr. Zheng also serves as the Director of Gynecologic Pathology service and the Director of Gynecologic Pathology Fellowship at the UTSW Medical Center.

Dr. Zheng earned his medical degree at Shanghai Medical College Fudan University. He completed a residency in obstetrics and gynecology at the Hospital of Obstetrics and Gynecology in Shanghai and, later, a residency in anatomic and clinical pathology at New York Hospital-Cornell Medical Center. He received advanced training through a gynecologic pathology fellowship at Women & Infants Hospital of Rhode Island and a research fellowship in molecular reproductive medicine at Columbia University College of Physicians and Surgeons (New York).

Dr. Zheng runs an active consultation practice that receives material world wide. Dr. Zheng has published more than 180 peer-reviewed articles in high impact scientific journals, mostly in the field of gynecologic pathology. He has served in various editorial capacities for over 50 journals, and is currently an editorial board member for multiple journals in the biomedical sciences. His main research contributions include endometrial serous carcinogenesis and precancerous lesion endometrial glandular dysplasia, cell origin of low-grade

ovarian serous carcinoma, molecular mechanism of progestin resistance in endometrial cancer and its precancers, hormonal etiology of ovarian epithelial cancers, and tubal contribution of ovarian endometriosis and its associated ovarian cancers. In addition, Dr. Zheng has created a novel approach called one-stop cervical care (OSCC) to diagnose and treat cervical pre-cancers. Dr. Zheng Loves teaching gynecologic pathology to residents and fellows and have taught numerous gynecologic pathology courses nationally and internationally.

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Uterine Mesenchymal Lesions

1

Brooke E. Howitt and Marisa R. Nucci

Abstract

This chapter will cover the pathology of uterine mesenchymal tumors, including endometrial stromal neoplasms, undifferentiated uterine sarcomas, uterine tumors resembling ovarian sex cord-stromal tumors (UTROSCT), smooth muscle tumors, perivascular epithelioid cell tumor (PEComa), Mullerian adenosarcoma, and inflammatory myofibroblastic tumor, as well as some less common mesenchymal tumors that may be encountered in the uterus. The salient histopathologic, immunophenotypic, as well as molecular findings that help separate these different tumor types will be discussed.

Keywords

Leiomyoma · Leiomyosarcoma · Endometrial stromal tumor · Endometrial stromal sarcoma · PEComa · Inflammatory myofibroblastic tumor · Adenosarcoma · Uterine tumor resembling ovarian sex cord-stromal tumor

1.1 Introduction

This chapter will cover the pathology of uterine mesenchymal tumors, including endometrial stromal neoplasms, undifferentiated uterine sarcomas, uterine tumors resembling ovarian sex cord-stromal tumors (UTROSCT), smooth muscle tumors, perivascular epithelioid cell tumor (PEComa), Mullerian adenosarcoma, and inflammatory myofibroblastic tumor, as well as some less common mesenchymal tumors that may be encountered in the uterus. The salient histopathologic, immunophenotypic, as well as molecular findings that help separate these different tumor types will be discussed.

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1.2 Endometrial Stromal Tumors (ESTs)

Currently, the World Health Organization (WHO) recognizes four main categories of endometrial stromal tumors: (1) endometrial stromal nodule, (2) low-grade endometrial stromal sarcoma, (3) high-grade endometrial stromal sarcoma, and (4) undifferentiated uterine sarcoma. High-grade endometrial stromal sarcoma is now recognized as a distinct entity largely due to its unique histology, clinical behavior, and underlying molecular alterations [1, 2]. Additional molecularly defined "high-grade uterine sarcomas" with alterations in the gene *BCOR* have more recently been described and thus have not been formally adopted into the WHO categorization of endometrial stromal tumors and therefore will be discussed separately.

1.2.1 Endometrial Stromal Nodule

1.2.1.1 Definition

Endometrial stromal nodule (ESN) is defined as an endometrial stromal neoplasm with no or minimal myometrial invasion and no vascular invasion.

1.2.1.2 Clinical Features

Endometrial stromal nodules (ESN) are benign neoplasms that occur across a very wide age range but are most frequently encountered in women in their fifth to sixth decades [3–6].

1.2.1.3 Gross Findings

ESN may be located at the submucosal layer of the uterine wall, project into the endometrial cavity as an exophytic

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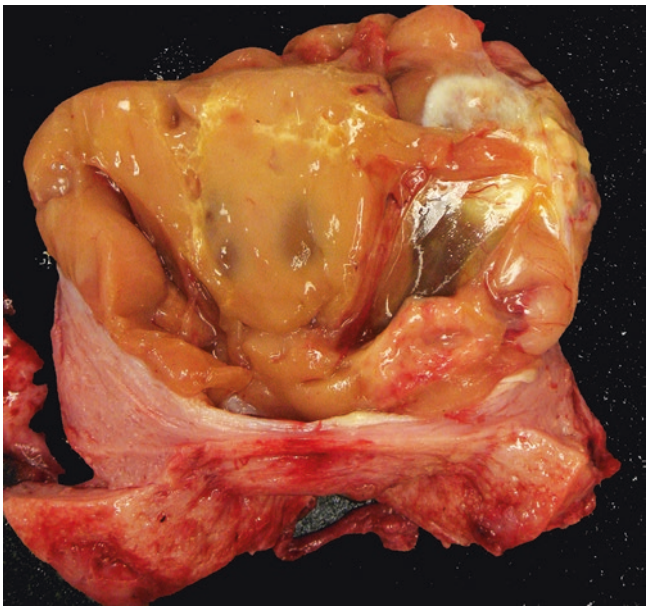

Fig. 1.1 Endometrial stromal nodule. Endometrial stromal nodules are well circumscribed, and typically soft in consistency and yellow to tan in coloration. This example also shows some cystic change

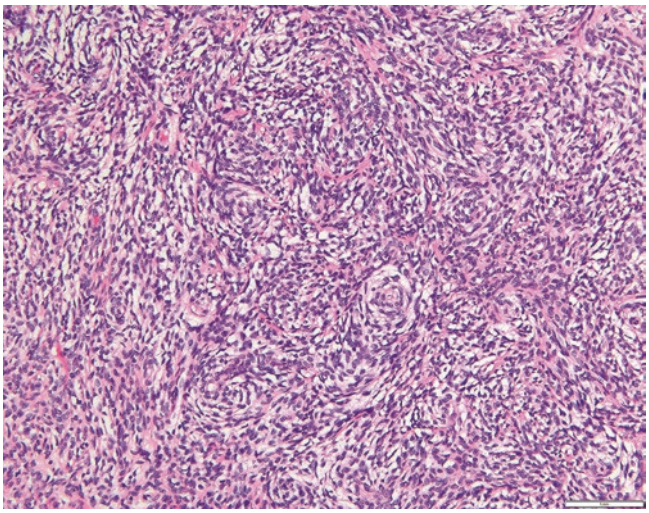

Fig. 1.2 Endometrial stromal nodule. This is an example of an endometrial stromal nodule, composed of cells with bland fusiform nuclei, often forming whorls around small arteriole-like vessels. These high-power cytologic features are indistinguishable from a low-grade endometrial stromal sarcoma

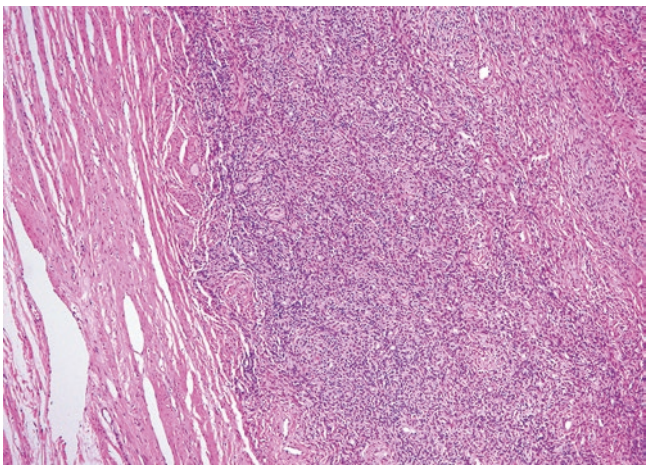

Fig. 1.3 Endometrial stromal nodule. Microscopically, endometrial stromal nodules typically are sharply demarcated from the surrounding myometrium without infiltrative borders

mass, or occur deep within the myometrium with no apparent connection to the endometrium. On gross examination, they are well circumscribed and may be mistaken for a leiomyoma; however, ESNs are usually softer in consistency and less rubbery without a bulging cut surface. Additionally, ESNs tend to be more yellow in coloration (Fig. 1.1). Hemorrhage and cystic degeneration may be seen. Endometrial stromal nodules can vary in size but are usually <10 cm, though larger tumors have been described [3, 5, 7, 8]. It is important to note that the border of ESN with the surrounding myometrium must be entirely submitted for histologic examination to exclude microscopic infiltration.

1.2.1.4 Microscopic Findings

Histologically, ESN are well-circumscribed but unencapsulated tumors resembling the nonneoplastic stroma of proliferative endometrium, composed of cells with uniform round to ovoid/fusiform nuclei that have scant to moderate amounts of eosinophilic to amphophilic cytoplasm. These cells appear to whorl around a prominent vascular component, which resembles spiral arterioles of nonneoplastic endometrium (Fig. 1.2). The vessels are typically evenly spaced and uniform in caliber throughout the neoplasm. In a minority of cases, larger, thick-walled vessels may be focally present and are usually located at the periphery. ESN is characterized by sharp circumscription between the tumor nodule and surrounding tissue (endometrium or myometrium) (Fig. 1.3). Sometimes there may be some slight irregularity to the border in the form of small lobulated or fingerlike extensions into the surrounding myometrium (Fig. 1.4) [3]. However in ESN no vascular invasion is present, and any irregular foci at the myometrial interface must be <3 in number, and each of these foci should extend <3 mm from the main mass [3]. ESN may demonstrate variant morphology, including smooth muscle and sex cord-like differentiation, making the diagnosis more challenging [6, 9, 10] (discussed in more detail in the low-grade endometrial stromal sarcoma (LGESS) variant morphology section).

Occasionally, some endometrial stromal tumors are predominantly well-circumscribed but exhibit greater than 3 mm extension into the surrounding myometrium yet also lack the typical overt myometrial permeation seen in endometrial stromal sarcoma. The term "endometrial stromal

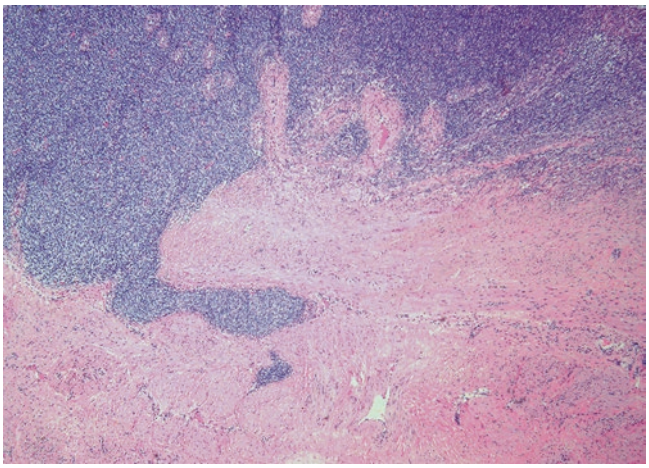

Fig. 1.4 Endometrial stromal tumor with limited infiltration. Some endometrial stromal neoplasms have predominantly well-circumscribed borders but may show a limited amount of permeative, fingerlike projection into the myometrium. When these measure >3 mm from the main mass and are >3 in number, these tumors are classified as endometrial stromal tumors with limited infiltration

tumor with limited infiltration" has been proposed for such tumors [6]. Given that very few cases have been described and all have been treated by hysterectomy, the long-term biologic potential and natural history is not known [6]. In practice, we recommend diagnosing these as "endometrial stromal sarcoma with limited infiltration" or "endometrial stromal neoplasm with limited infiltration" with a comment suggesting that the tumor may pursue a benign clinical course but clinical follow-up is nevertheless recommended.

1.2.1.5 Biomarkers

Similar to nonneoplastic endometrial stroma, ESNs are virtually always positive for CD10 and PR by immunohistochemistry and are otherwise nearly identical immunophenotypically to LGESS.

1.2.1.6 Differential Diagnosis

One of the most important considerations in the differential diagnosis of ESN is that of LGESS, which is a malignant tumor. ESN and LGESS are distinguished entirely by histologic features, specifically pattern of growth/border with myometrium and presence or absence of lymphovascular invasion [2, 6, 11]. In some cases, there may be limited infiltration of the myometrium, comprising a gray area diagnostically. As discussed above, such tumors are classified as "endometrial stromal neoplasm with limited infiltration." Of note, ESN cannot be distinguished from LGESS by immunohistochemical or molecular methods.

Another entity that may be confused with ESN is highly cellular leiomyoma (HCL). HCL is characterized by a dense, hypercellular spindled stroma but contains characteristic intratumoral thick-walled vessels which are not common in endometrial stromal neoplasms. Similarly, HCL like other smooth muscle neoplasms frequently have prominent cleft-like spaces that are not a feature of ESN/LGESS. It is important to be aware that while immunohistochemistry may be helpful in this distinction by the finding of strong diffuse caldesmon and desmin positivity and CD10 negativity, many examples of HCL may be CD10 positive and also have less strong/diffuse staining for caldesmon/desmin than conventional leiomyomas [12]. Furthermore, endometrial stromal tumors may have morphologic and immunophenotypic evidence of smooth muscle differentiation so correlation of the immunohistochemical findings with the morphology is critical. Regarding the concept of stromomyoma or endometrial stromal lesion with smooth muscle differentiation, please refer to the section of LGESS below.

1.2.1.7 Genetic Profile

The genetic profile of ESN is nearly identical to that in LGESS and thus will be discussed below under LGESS. Briefly, ESN is characterized by frequent translocations involving *JAZF1*.

1.2.1.8 Management and Outcome

Most women with ESN have been treated by hysterectomy, in part because they may be an incidental finding in hysterectomy specimens but also due to the difficulty in distinguishing between ESN and LGESS in biopsy or curettage samplings which often triggers hysterectomy. If fertility preservation is desired, this might be possible with resection of the nodule to include the mass and a rim of myometrium to assess for invasion but is dependent on tumor size or location within the uterus. Although few women with ESN have been treated conservatively (i.e., local excision without complete hysterectomy), none of the reported patients have recurred [3, 6].

1.2.2 Endometrial Stromal Sarcoma (Low-Grade)

1.2.2.1 Definition

A malignant tumor composed of cells resembling nonneoplastic endometrial stroma, with invasion into surrounding myometrium and/or vascular invasion

1.2.2.2 Clinical Features

LGESS occur over a wide age range but are most commonly encountered in the perimenopausal and postmenopausal period, with a mean age at presentation of 52 years [13]. Though ESS comprise <1% of all uterine malignancies, they are the second most common uterine sarcoma [14]. Typically, patients with LGESS present with abnormal uterine bleeding, postmenopausal bleeding, or pain; less commonly a

mass or uterine enlargement may be palpated. In about one third of cases, clinical presentation may be related to signs or symptoms related to metastatic disease.

1.2.2.3 Gross Findings

LGESS may present as an intracavitary or intramural uterine mass and can appear well-circumscribed or with overt myometrial infiltration with tonguelike extensions and wormlike intravascular tumor plugs (Fig. 1.5) [7]. The cut surface is generally tan to yellow and hemorrhage may be apparent. Necrosis is less commonly identified grossly.

1.2.2.4 Microscopic Findings and Histologic Grading

Histologically, the tumor cells resemble nonneoplastic proliferative-phase endometrial stroma and appear virtually identical to ESN. However, LGESS by definition exhibits prominent fingerlike penetration of the myometrium and/or lymphovascular invasion, in contrast to ESN (Fig. 1.6). Hyaline bands and plaques are commonly encountered in LGESS but are not a specific finding (Fig. 1.7a). Foamy histiocytes, either singly or in clusters, may be seen in LGESS (Fig. 1.7b). Less commonly encountered morphologic features include extensive myxoid change and a prominent fibrous stroma.

1.2.2.5 Biomarkers

CD10 was recognized as a potential marker of endometrial stromal differentiation based on its high expression in LGESS [15–18]. It is now well known that CD10 is expressed in endometrial stromal cells including those in eutopic endometrium, adenomyosis, and endometriosis in addition to ESN and LGESS [18, 19]. CD10 is typically strongly and diffusely positive in nonneoplastic and neoplastic endometrial stroma (Fig. 1.8a); however, some endometrial stromal tumors may be negative for this marker [20–22]. Another marker of

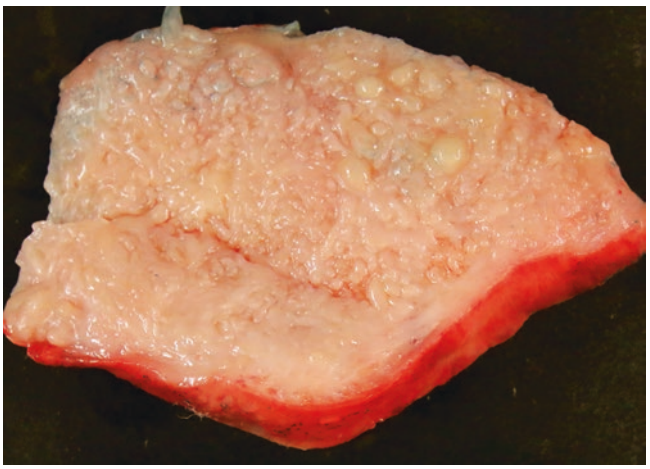

Fig. 1.5 Low-grade endometrial stromal sarcoma, gross appearance. Endometrial stromal sarcoma is a tan to yellow mass with nodular "wormlike" growth through the myometrium

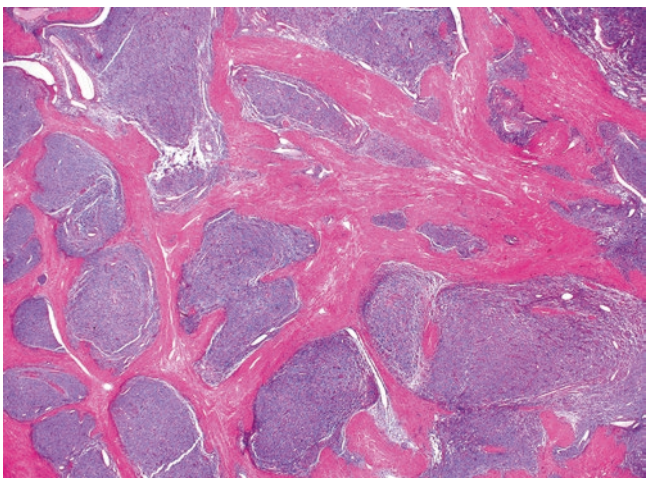

Fig. 1.6 Low-grade endometrial stromal sarcoma. From low-power microscopic examination, the permeative fingerlike pattern of infiltration into the myometrium is apparent

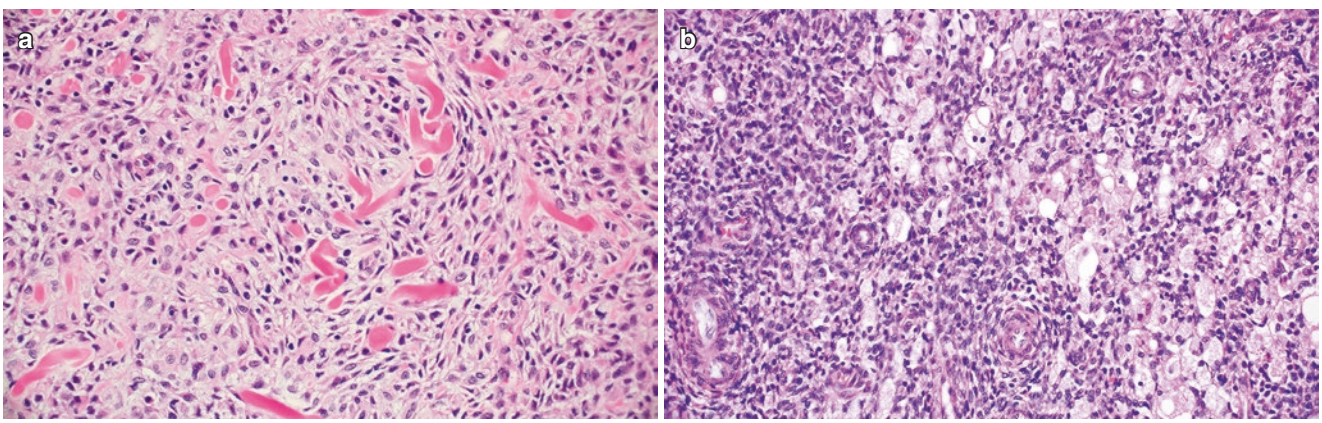

Fig. 1.7 Low-grade endometrial stromal sarcoma histologic features. (**a**) Endometrial stromal neoplasms frequently have hyaline plaques or bands, but this is not specific to this entity. (**b**) Foamy histiocytes may also be present in small numbers or large aggregates in endometrial stromal neoplasms

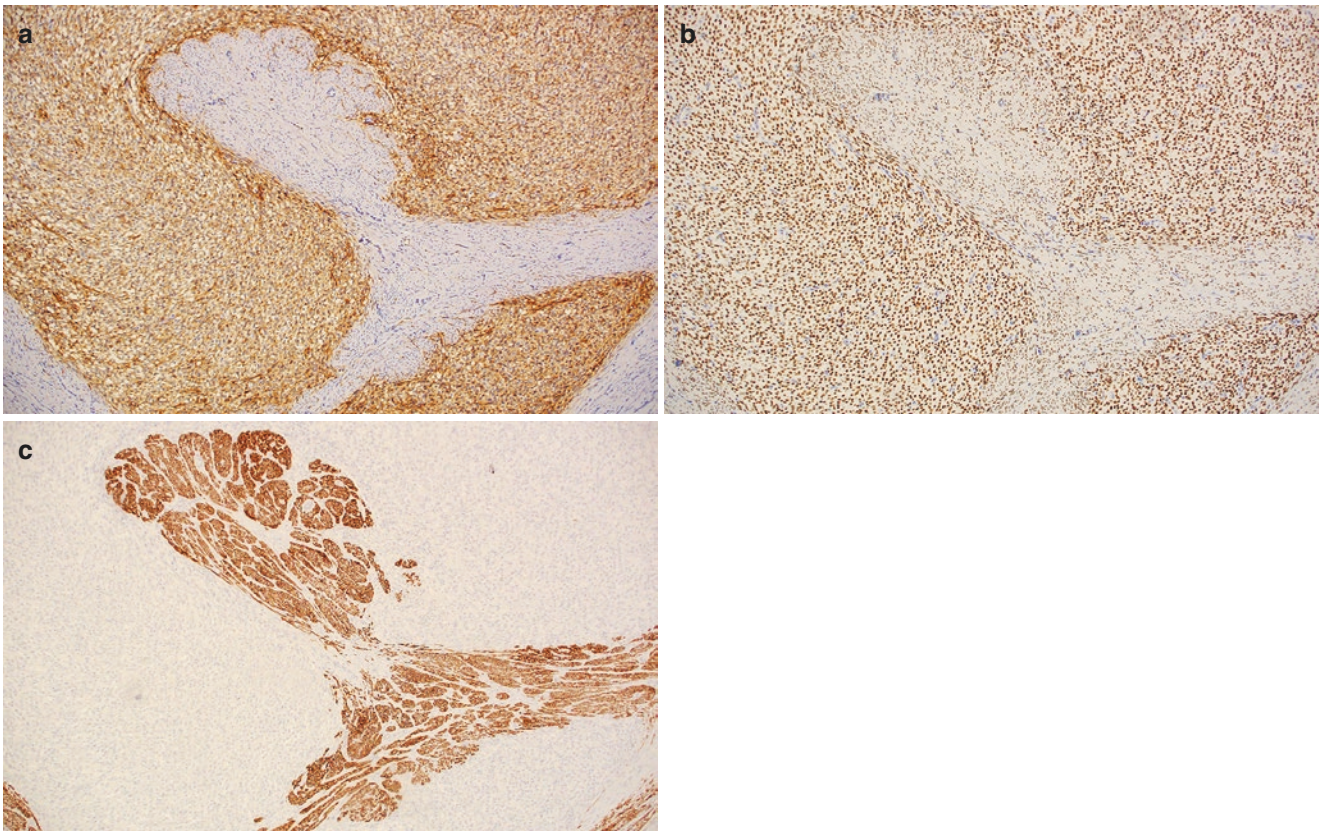

Fig. 1.8 Low-grade endometrial stromal sarcoma immunohistochemistry. (**a**) CD10 is almost always positive in LGESS (as well as ESN). (**b**) The hormone receptors estrogen receptor and progesterone receptor are typically strongly positive in low-grade endometrial stromal neoplasms. (**c**) Desmin is typically negative in endometrial stromal neoplasms; however, it may be positive in areas of smooth muscle differentiation

endometrial stromal differentiation is the novel marker interferon-induced transmembrane protein 1 (IFITM1) which has shown to be a sensitive and specific marker for endometrial stromal tumors and is also highly expressed in nonneoplastic endometrial stroma [23]. Endometrial stromal tumors are generally positive for ER and PR (Fig. 1.8b) and negative for smooth muscle markers (Fig. 1.8c); however desmin positivity has been documented in otherwise conventional appearing ESTs, while caldesmon appears to be specific for smooth muscle differentiation. p53 is generally wild type in LGESS. Nuclear beta-catenin is frequently expressed in both ESN and LGESS [24].

1.2.2.6 Variants of Endometrial Stromal Tumors

Both ESN and LGESS may exhibit a wide range of altered differentiation, including smooth muscle, sex cord-like, and epithelial (endometrioid-type glands); very rarely skeletal muscle differentiation may be seen [4, 9, 10, 25–27]. Extensive stromal hyalinization secondary to increased collagenous matrix production may impart a fibroblastic appearance. However, in general, other areas with typical endometrial stromal morphology are usually present. In addition, the characteristic vascular component and arrangement of the tumor cells around them are maintained [28, 29]. Other less common variant features include epithelioid morphology, clear or granular cytoplasm, bizarre atypia, pseudopapillary growth, ossification, osteoclast-like giant cells, and adipocytic metaplasia [27–32].

1.2.2.7 Endometrial Stromal Tumor with Endometrioid Glands

Uncommonly, LGESS may have foci of endometrioid glandular differentiation [30, 33]. Although divergent differentiation is the most likely explanation for their presence, some examples may represent entrapped nonneoplastic endometrial glands (Fig. 1.9). In general, this type of differentiation in LGESS is focal and the main differential diagnosis is the distinction from adenomyosis, particularly gland-poor adenomyosis, which only rarely forms a distinct grossly apparent mass [34].

1.2.2.8 Endometrial Stromal Tumor with Smooth Muscle Differentiation

ESN/LGESS with smooth muscle differentiation are not common but are a source of confusion in the recognition and diagnosis of endometrial stromal tumors [10, 26]. If the smooth muscle component comprises more than 30% of the tumor, then they are considered by some to be mixed endometrial stromal-smooth muscle tumors [10]; however, many

prefer to use the terminology ESN with smooth muscle differentiation or LGESS with smooth muscle differentiation. Historically these tumors may have been called "stromomyoma." Histologic features of smooth muscle differentiation include typical smooth muscle morphology reminiscent of that seen in leiomyomata (Fig. 1.10a), nodules with central prominent hyalinization, or irregular islands that can be either discrete or merge imperceptibly with the areas characteristic of stromal differentiation (Fig. 1.10b). These tumors have been shown to be of endometrial stromal derivation by molecular analyses; therefore, determination of benign versus malignant should be made using the criteria for endometrial stromal tumors [10]. Immunohistochemically, areas of smooth muscle differentiation within an endometrial stromal tumor will stain identically to smooth muscle tumors, while areas of conventional endometrial stromal appearance should be negative for caldesmon but may be variably positive for desmin. CD10 is not entirely specific and may be expressed in the smooth muscle component.

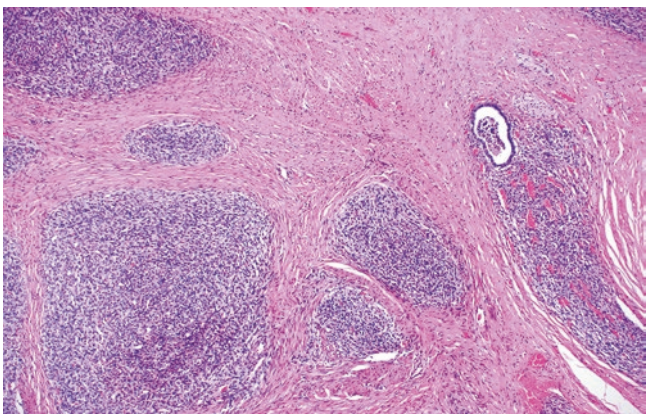

Fig. 1.9 Low-grade endometrial stromal sarcoma with endometrioid glands. The infiltrative pattern of this tumor is apparent, and focally there is a benign-appearing endometrioid gland within the LGESS

1.2.2.9 Endometrial Stromal Tumor with Sex Cord-Like Elements

LGESS/ESN may contain variable amounts of sex cord-like elements, typically resembling ovarian granulosa cell or Sertoli cell tumors (Fig. 1.11a, b). This finding is seen in up

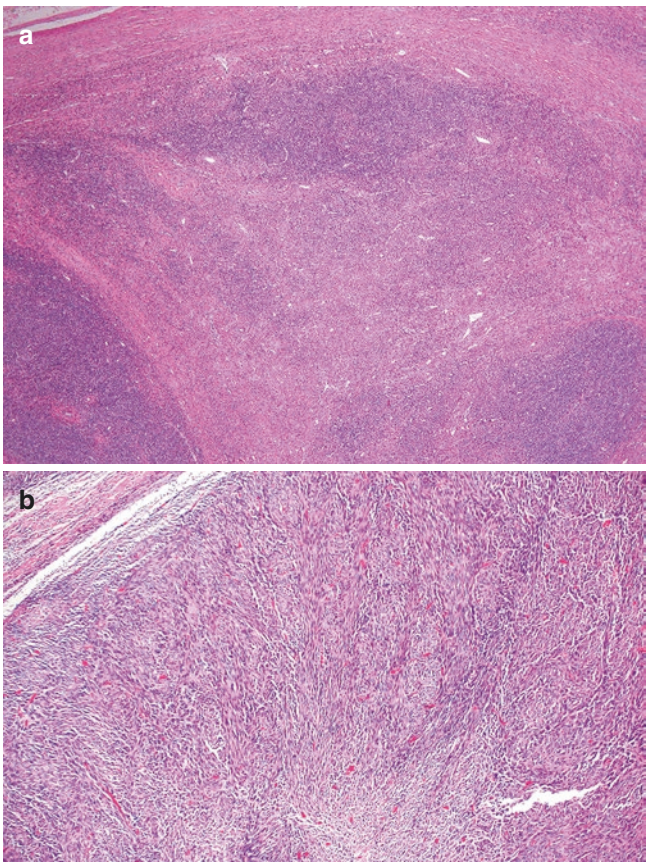

Fig. 1.10 Endometrial stromal tumors with smooth muscle differentiation. Both endometrial stromal nodule (**a**) and low-grade endometrial stromal sarcoma (**b**) may demonstrate varying amounts of smooth muscle differentiation

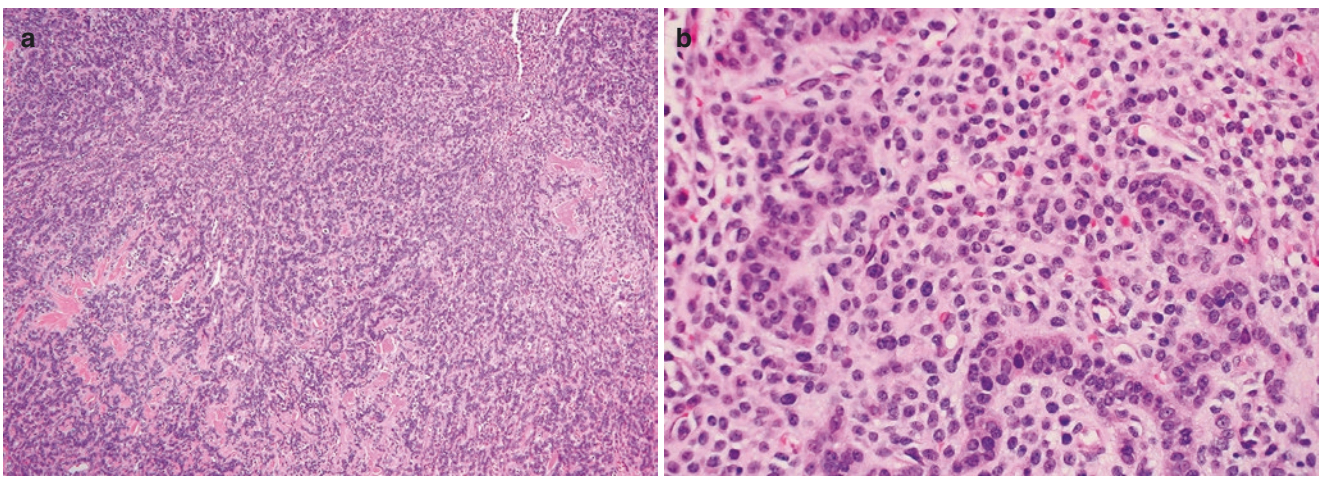

Fig. 1.11 Low-grade endometrial stromal sarcoma with sex cord differentiation. Endometrial stromal tumors may have variant sex cord differentiation (**a**). Typically, this is in the form of cords and trabeculae resembling granulosa cell or Sertoli cell tumor (**b**)

to 60% of endometrial stromal tumors and may coexist with smooth muscle differentiation. The presence of sex cord-like differentiation in ESN and LGESS does not appear to have an impact on clinical behavior. Histopathologic criteria for the distinction between a stromal nodule and stromal sarcoma, as outlined previously, are applied regardless of the presence of sex cord-like elements. Immunohistochemically, the sex cord-like elements will stain for typical sex cord markers (e.g., inhibin, calretinin, CD99) only in the areas of sex cord differentiation. The background endometrial stromal tumor will typically not be positive for these markers.

1.2.2.10 Genetic Profile

Chromosomal rearrangements involving chromosomes 6, 7, and 17 are the most frequent cytogenetic abnormalities that have been reported in both LGESS and ESN, with *JAZF1-SUZ12* being the most common gene fusion identified (reported frequency ranges from 25% to >90% depending on the study design and tumor morphology) [32, 35–41]. This gene fusion reflects the chromosomal translocation t(7;17)(p15;q21) or related variant translocations frequently observed in LGESS via conventional cytogenetics or FISH. In ESN, one study has demonstrated that the non-rearranged *JAZF1* allele is transcriptionally active in ESN, but in ESS it appears to be silenced [42], suggesting that epigenetic changes play a role in LGESS pathogenesis. Another translocation involving *JAZF1*, t(6;7)(p21;p15), resulting in a *JAZF1-PHF1* gene fusion, is present in up to 28% of ESS [41, 43–45]. LGESS with *PHF1* rearrangement is enriched for sex cord-like differentiation [43, 45] but also may show myxoid morphology, smooth muscle differentiation, or typical morphology [46]. In tumors lacking *JAZF1* abnormalities, *PHF1* has been also been found to be recurrently involved in another chromosomal translocation and resultant gene fusion with *MEAF6* [47, 48]. Other partners of *PHF1* described in LGESS include *EPC1*, *BRD8*, and *EPC2* [49]. A subset of LGESS with conventional karyotyping have no evidence of chromosomal rearrangements as well as no evidence of *JAZF1* or *PHF1* gene fusions by RT-PCR or FISH, suggesting that some of the molecular alterations in these tumors have not yet been discovered or may be too small to detect with these methods. In addition, FISH studies of mixed endometrial stromal-smooth muscle tumors show evidence for the *JAZF1* gene rearrangement in both the endometrial stromal component and smooth muscle component, supporting the concept that these tumors are of endometrial stromal derivation [38, 40]. Rarely, LGESS can show *MDM2* amplification by FISH as well as MDM2 protein expression by immunohistochemistry [50].

1.2.2.11 Differential Diagnosis

Endometrial stromal tumors with smooth muscle differentiation or those that have a fibrous or myxoid appearance may be confused with uterine smooth muscle tumors [10, 20, 27, 28, 51]. Conversely, uterine smooth muscle tumors may mimic endometrial stromal tumors, particularly when the former is markedly cellular (e.g., highly cellular leiomyoma) or has prominent vascular invasion (e.g., intravascular leiomyomatosis, IVL) [8, 52–55]. In general, the morphologic appearance of tumor cells and the growth pattern within the myometrium can distinguish LGESS from leiomyosarcoma. In contrast to leiomyosarcoma, areas of smooth muscle differentiation in LGESS tend to be bland and will not exhibit the degree of cellularity and nuclear pleomorphism that is frequently encountered in leiomyosarcoma. In cases in which there is prominent lymphatic or vascular permeation by leiomyosarcoma, morphologic features such as the presence of fascicular growth even in the intravascular component help facilitate its recognition as a malignant smooth muscle tumor. In addition, a panel of antibodies including caldesmon, desmin, and CD10 may be helpful in difficult cases, provided one is aware of the potential pitfalls. ESN/LGESS are at most only focally positive for smooth muscle actin and desmin in most cases; however, a subset of morphologically typical cases may show more extensive expression of these markers [9, 10, 28, 56–58]. In contrast, caldesmon is a more specific marker of smooth muscle differentiation than desmin and may be useful in this differential [56, 59]. In the distinction between intravenous leiomyomatosis and LGESS, the histologic features suggestive of smooth muscle in the former including vasculature and clefting may be helpful. Additionally, the nuclei of smooth muscle tumors tend to be blunted ("cigar-shaped") rather than delicately ovoid or fusiform as in endometrial stromal tumors. One pitfall to keep in mind is that caldesmon may, in some cases of highly cellular smooth muscle neoplasms, including cellular IVL, only show patchy or focal positivity [56]. One study has shown that IFITM1 may be a more specific marker of endometrial stromal differentiation in the distinction from smooth muscle tumors [60]. Similarly, nuclear beta-catenin staining is supportive of EST diagnosis over a smooth muscle tumor in one study [24]. If there is a question diagnostically, FISH for *JAZF1* rearrangement may be performed.

Endometrial stromal tumors with sex cord-like differentiation must be distinguished from uterine tumors resembling ovarian sex cord tumor (UTROSCT). In the initial description of UTROSCT, all endometrial stromal tumors with sex cord elements were divided into group I or group II based on the percent of sex cord elements present in the tumor, with group I containing only focal sex cord elements and group II a predominance [61]. Since that time, it has been recognized that group I represents endometrial stromal tumors with sex cord-like elements while group II represents UTROSCT (see later section). The finding of conventional endometrial stromal neoplasia is the distinguishing feature

of LGESS/ESN, but may not be present or be difficult to identify in biopsy or curettage specimens.

Consideration of the differential diagnosis of LGESS versus HGESS is discussed in the HGESS section.

1.2.2.12 Management and Outcomes

Patients with LGESS are treated by hysterectomy and bilateral salpingo-oophorectomy. Patients with tumors confined to the uterus (stage I) have an excellent prognosis, with a 5-year survival rate over 90% [7, 62]. However, recurrence may occur in up to 25% of patients with stage I disease [7, 63]. Poor prognostic indicators within stage I disease include older patient age and tumor size [62]. Unfortunately, there are no histopathologic or molecular parameters to predict which patients with tumors confined to the uterus are at risk for recurrence. Distant metastases, frequently involving the lung, may occur and may occur late, nearly a decade following initial diagnosis [64]. Tumors that are high stage at presentation (stage III/IV) have a significantly worse prognosis, with only 50% 5-year survival [65]. After surgery, adjuvant treatment options include local radiation therapy. There is no evidence that chemotherapy or radiotherapy has any impact on long-term survival [63]. Given that LGESS is typically positive for PR, hormonal therapy is an option that may be considered in patients who present with advanced-stage disease or have recurrences.

1.2.3 High-Grade Endometrial Stromal Sarcoma (HGESS)

1.2.3.1 Definition

The discovery of *YWHAE-NUTM2A/B* gene fusions in a subset of endometrial stromal sarcomas, which are associated with a clinical outcome intermediate between that of LGESS and undifferentiated uterine sarcoma, has led to the reintroduction of HGESS in the most recent WHO classification [2, 66, 67]. HGESS is a malignant tumor of endometrial stromal derivation, with variable morphology but typically containing at least a focal characteristic round cell component.

1.2.3.2 Clinical Features

Patients often present with similar symptoms to other uterine sarcomas, with abnormal uterine bleeding and/or a palpable uterine mass; however, unlike LGESS, patients with HGESS typically present with advanced-stage disease (stages III–IV >> stage I) [68].

1.2.3.3 Gross Findings

HGESS grossly may appear very similar to LGESS, with either an intracavitary or intramural fleshy tan to yellow mass (Fig. 1.12); however, necrosis and/or hemorrhage is more common.

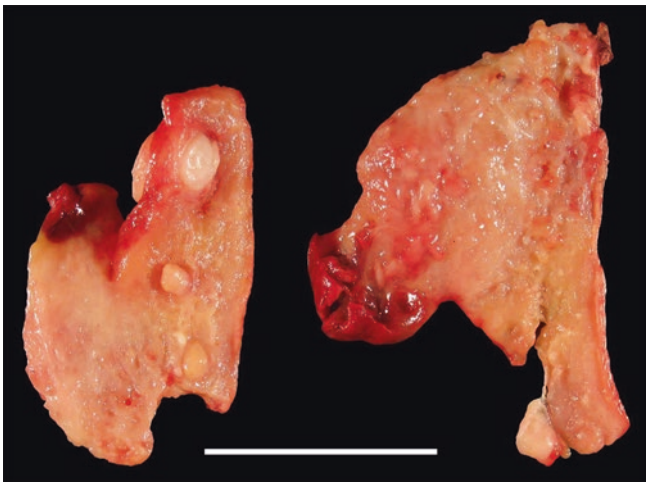

Fig. 1.12 High-grade endometrial stromal sarcoma, gross appearance. High-grade endometrial stromal sarcoma may appear very similar to low-grade stromal sarcoma on macroscopic examination, with a soft, fleshy consistency, yellow to tan color, and "wormlike" infiltration of the myometrium

1.2.3.4 Microscopic Findings and Histologic Grading

HGESS have high-grade, but uniform, cytologic atypia and tend to lack the typical morphology of LGESS in that they do not closely resemble nonneoplastic endometrium. In some cases HGESS may be associated with more typical appearing areas of LGESS [69, 70] and, in very rare cases, may be composed of low-grade morphology entirely [68, 71]. HGESS typically has a nodular permeative growth within the myometrium; however, destructive myometrial infiltration may also be seen (Fig. 1.13a). Moreover, the background vascular pattern is different; HGESS has numerous delicate and arborizing vessels as opposed to the spiral arteriolar-like vascular network of LGESS (Fig. 1.13b). In the high-grade areas, the tumor cells are epithelioid with moderate to scant amount of variably eosinophilic cytoplasm and rounded nuclei with conspicuous nucleoli. Mitotic activity is frequently brisk, >10 per 10 HPFs and tumor necrosis is not uncommon. The low-grade components, when present, may have typical LGESS morphology but is also highly enriched for the fibromyxoid variant.

1.2.3.5 Biomarkers

HGESS has a distinctly different immunohistochemical profile from that seen in LGESS, typically with a CD10−/cyclin D1+ (>70% of tumor nuclei)/ER−/PR− pattern in the morphologically high-grade areas [70]. In cases with both histologic low- and high-grade components, different patterns of staining may be seen in the morphologically low-grade versus high-grade component, with the low-grade component showing positivity for CD10, ER, and PR and only patchy positivity (usually weak and focal) for cyclin D1 [70]. In