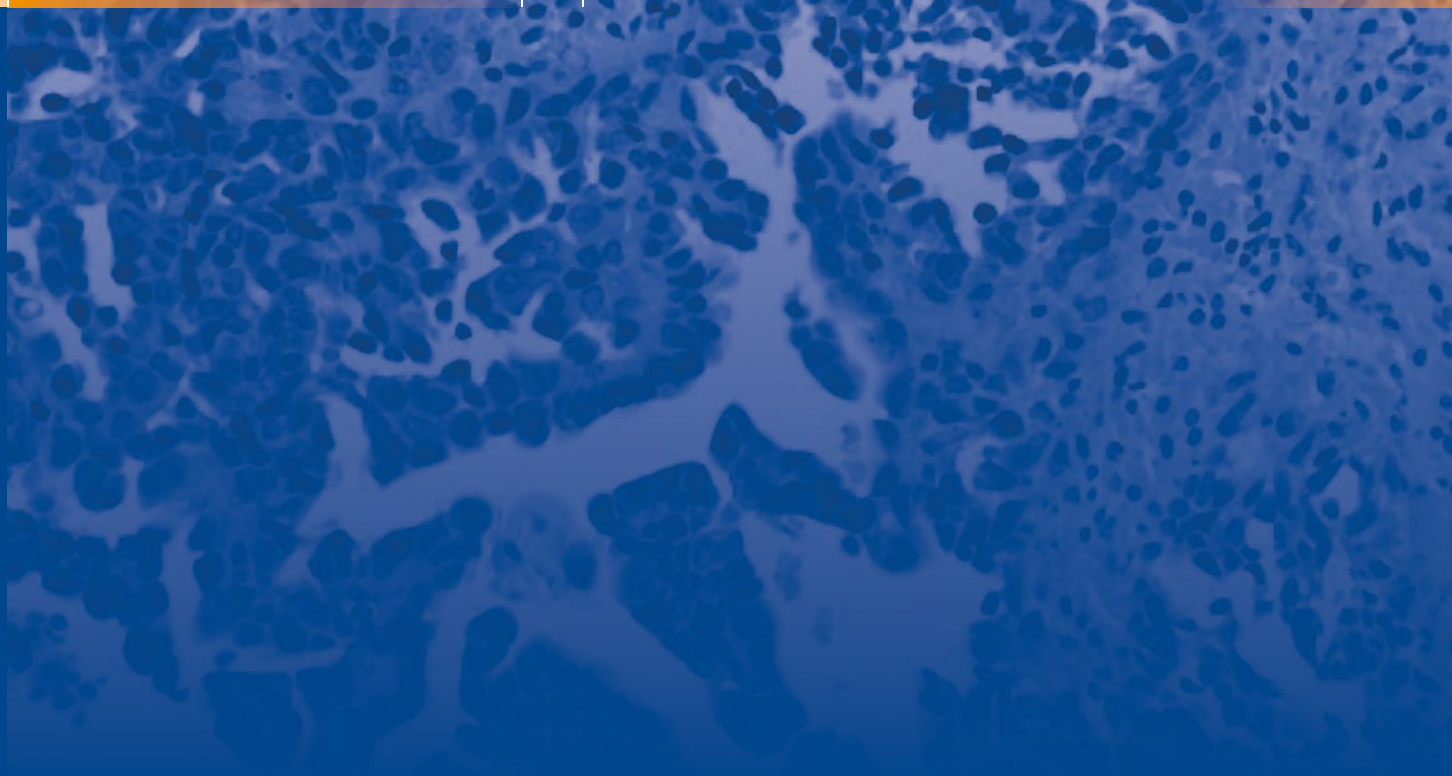
Oluwole Fadare
Andres A. Roma

Atlas of Uterine Pathology



Springer

Atlas of Anatomic Pathology

Series Editor

Liang Cheng
Indianapolis, IN, USA

Oluwole Fadare • Andres A. Roma

Atlas of Uterine Pathology

Springer

Oluwole Fadare
University of California, San Diego
La Jolla, CA
USA

Andres A. Roma
University of California, San Diego
La Jolla, CA
USA

ISSN 2625-3372 ISSN 2625-3380 (electronic)
Atlas of Anatomic Pathology
ISBN 978-3-030-17930-4 ISBN 978-3-030-17931-1 (eBook)
https://doi.org/10.1007/978-3-030-17931-1

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

I dedicate this book to the memory of my mother, Alhaja Ajoke Iyabo Fadare, RPh (1948–2019), in complete appreciation for everything she embodied and imparted, and in celebration of her cherished legacy.

Oluwole Fadare

Dedicated to my father and mentors who pushed me to be the best version of myself.

Andres A. Roma

Series Preface

One Picture Is Worth Ten Thousand Words

— Frederick Barnard, 1927

Remarkable progress has been made in anatomic and surgical pathology during the last 10 years. The ability of surgical pathologists to reach a definite diagnosis is now enhanced by immunohistochemical and molecular techniques. Many new clinically important histopathologic entities and variants have been described using these techniques. Established diagnostic entities are more fully defined for virtually every organ system. The emergence of personalized medicine has also created a paradigm shift in surgical pathology. Both promptness and precision are required of modern pathologists. Newer diagnostic tests in anatomic pathology, however, cannot benefit the patient unless the pathologist recognizes the lesion and requests the necessary special studies. An up-to-date Atlas encompassing the full spectrum of benign and malignant lesions, their variants, and evidence-based diagnostic criteria for each organ system is needed. This Atlas is not intended as a comprehensive source of detailed clinical information concerning the entities shown. Clinical and therapeutic guidelines are served admirably by a large number of excellent textbooks. This Atlas, however, is intended as a "first knowledge base" in the quest for definitive and efficient diagnosis of both usual and unusual diseases.

The Atlas of Anatomic Pathology is presented to the reader as a quick reference guide for diagnosis and classification of benign, congenital, inflammatory, nonneoplastic, and neoplastic lesions organized by organ systems. Normal and variations of "normal" histology are illustrated for each organ. The Atlas focuses on visual diagnostic criteria and differential diagnosis. The organization is intended to provide quick access to images and confirmatory tests for each specific organ or site. The Atlas adopts the well-known and widely accepted terminology, nomenclature, classification schemes, and staging algorithms.

This book series is intended chiefly for use by pathologists in training and practicing surgical pathologists in their daily practice. It is also a useful resource for medical students, cytotechnologists, pathologist assistants, and other medical professionals with special interest in anatomic pathology. We hope that our trainees, students, and readers at all levels of expertise will learn, understand, and gain insight into the pathophysiology of disease processes through this comprehensive resource. Macroscopic and histological images are aesthetically pleasing in many ways. We hope that the new series will serve as a virtual pathology museum for the edification of our readers.

More information about this series at http://www.springer.com/series/10144

Indianapolis, IN, USA — Liang Cheng

Preface

Every year, diseases of the uterus exert a significant burden to individual patients and, accordingly, to society at large. The prevention, diagnosis, treatment, and posttreatment monitoring for various uterine diseases will ultimately affect most adult women at some point in their lives. Many patients present with symptoms that are ultimately attributed to common uterine diseases such as uterine prolapse, adenomyosis, endometrial polyps, chronic endometritis, or dysfunctional uterine bleeding. Leiomyomas of the uterus remain the most common benign pelvic tumors in women, as well as the most common indication for hysterectomies in the United States. Many countries have large screening programs whose ultimate goal is to minimize the mortality associated with cervical cancers by detecting and eventually treating them at a precancerous phase or at an early stage. These screening programs affect large proportions of the population. Endometrial carcinomas are the most common malignancies of the female genital tract in Western countries and, along with cervical cancers, collectively account for approximately 75,000 new cancer cases diagnosed annually in the United States. Optimal management of the various uterine diseases is clearly one of the more significant functions of medicine as a discipline, and accurate pathologic diagnosis is integral to the entire process.

As with most other organs, pathology of the uterus evolves with time: new morphologic variants of classically known entities continue to be recognized; new biomarkers that purport to aid in diagnostic classification of neoplasms are regularly reported even as some older ones are reassessed; molecular profiles that may aid in diagnosis and/or prognosis are now well-known for several neoplasms; traditional tumor classification schemes are periodically reassessed to incorporate newly available information and to ensure that they achieve maximal prognostic and predictive stratification of the larger disease groups. Nonetheless, at present time, the practice of uterine surgical pathology is still largely based on the traditional tenets of the discipline, including a detailed assessment of morphologic features of a lesion, supplemented where applicable by its macroscopic and immunophenotypic profiles, and clinical correlation.

Our goal for this book is to present the broad morphologic spectrum of the most commonly encountered diseases of the uterine corpus and cervix in an easy-to-use, practically relevant format. Diseases are presented mostly as approximately 1200 images of the various entities. The book emphasizes the morphologic and immunophenotypic features of disease entities, with some additional coverage of normal histology, but is not meant to be a comprehensive treatise on all aspects of uterine surgical pathology. Short clinicopathologic summary descriptions are presented as figure legends for each entity, emphasizing the most salient information a diagnostic pathologist or trainee may wish to know. The image selection focuses on classical appearances as well as less common morphologic variations. Selected images that depict classical immunophenotypes are also presented. The information is broadly consistent with the entities that are recognized in the 2014 classification from the World Health Organization but is also inclusive of developments that have occurred in the subsequent 5 years, as well as the authors' experiences on and approaches to diagnostic classification.

The book is divided into 12 chapters that reflect broad clinicopathologic categorizations and presumed lines of differentiation, with chapters on uterine corpus diseases authored by Dr. Oluwole Fadare and chapters on uterine cervix diseases, as well as gestational trophoblastic

diseases authored by Dr. Andres Roma. Information about an individual disease entity is best located by referring to the subject index at the end of the book, or by browsing the chapter that is most likely to host that entity.

We are confident that this book will prove to be very useful to practitioners and trainees of uterine surgical pathology, as well as to clinicians and investigators interested in the morphology of uterine diseases.

La Jolla, CA, USA — Oluwole Fadare
La Jolla, CA, USA — Andres A. Roma

Contents

Normal Histology of the Uterine Corpus

1

1.1 Embryology and Normal Anatomy of the Uterine Corpus

The uterus is the fusion product of the embryologic paramesonephric (müllerian) ducts. By the second trimester, the endometrial lining is composed of columnar epithelium with surface ciliation, abundant nuclear pseudostratification, and occasional mitotic figures. The epithelium is mostly flat but may show undulations and gland-like invaginations into the underlying mesenchyme, in which a vague layering is often morphologically discernible (Figs. 1.1, 1.2, 1.3, 1.4, and 1.5).

The adult, non-gravid uterus is a pear-shaped structure that measures 7–9 cm on average along its long axis (Figs. 1.6 and 1.7). The caudal third of the uterus represents the cervix, and the proximal two thirds is the corpus [1–4]. The portion of the corpus cephalad to a line connecting the two fallopian tube origins is called the *fundus*. The body—the portion of the uterine corpus caudal to the same line—tapers into a lower uterine segment or uterine isthmus, which in turn is in continuity with the cervix. The uterine body is anteflexed on the cervix and the whole uterus is tipped slightly forward (anteversion). The hollow center of the uterus is a triangular space whose lining is continuous with the fallopian tube mucosa at the bilateral tubal cornu, and with the endocervical mucosa caudally. The endometrial cavity is lined by endometrium (comprising endometrial epithelium, endometrial mesenchyme, and vessels) and is surrounded by a myometrium composed of smooth muscle, vessels, and other mesenchymal elements. The myometrium comprises bundles of woven smooth muscle, which are arranged in two or three somewhat distinct layers, although this layering is not always clearly discernible. The outer portions of the myometrium are in continuity with the outer musculature of the fallopian tube, cervix, and vagina. The uterine musculature has a larger component of collagenous tissue at the level of the internal os and distally.

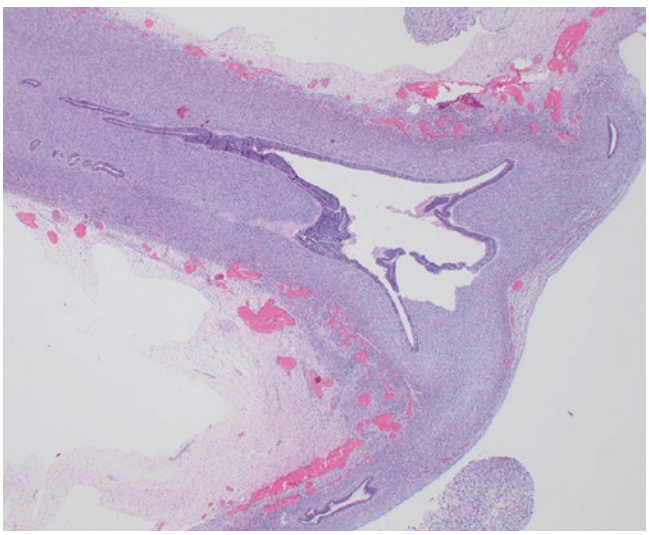


Fig. 1.1 Uterus at 18 weeks. Note the central epithelium-lined uterine canal surrounded by uterine mesenchyme

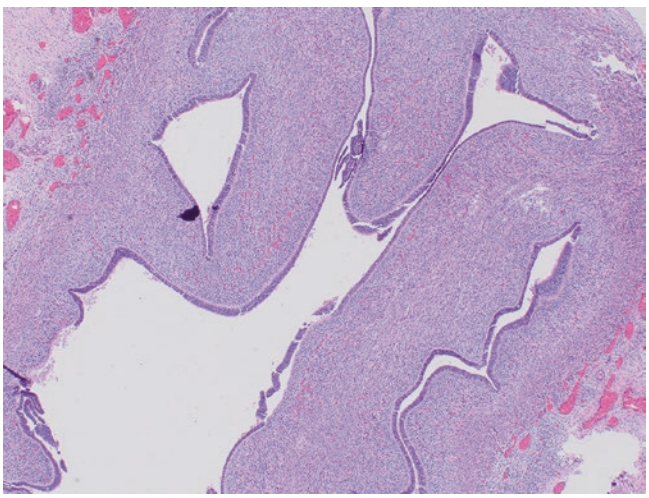


Fig. 1.2 Uterus at 22 weeks. The endometrial lining shows surface undulations and gland-like invaginations. Even at term, the endometrial lining is often simple and is devoid of the complex glandular architecture that may be encountered in the adult endometrium

O. Fadare, A. A. Roma, *Atlas of Uterine Pathology*, Atlas of Anatomic Pathology,
https://doi.org/10.1007/978-3-030-17931-1_1

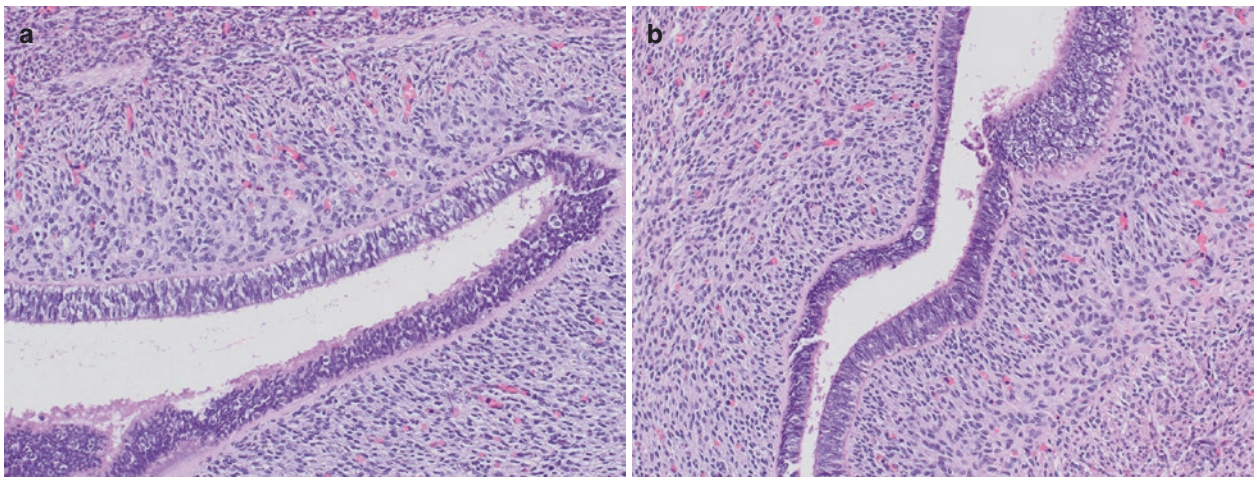


Fig. 1.3 (**a**, **b**) Uterus at 18 weeks. Endometrial epithelium shows ciliation and abundant pseudostratification. The surrounding mesenchyme shows vague layering and increased cellularity. Smooth muscle differentiation is demonstrable in the uterine mesenchyme at this stage

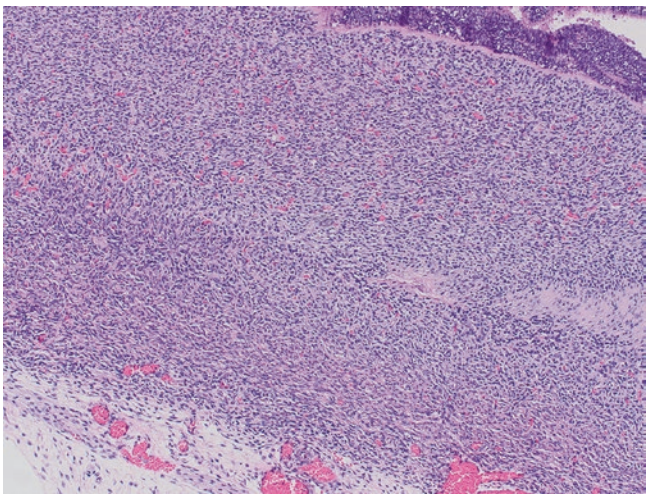


Fig. 1.4 Uterine mesenchyme at 23 weeks. A muscular layer is well developed. An outer layer (*lower field*) and inner layer are discernible. The endometrium epithelium is seen in the upper right field

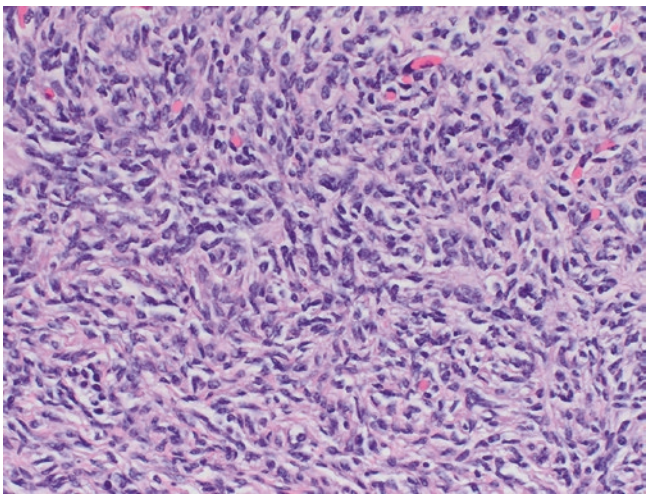
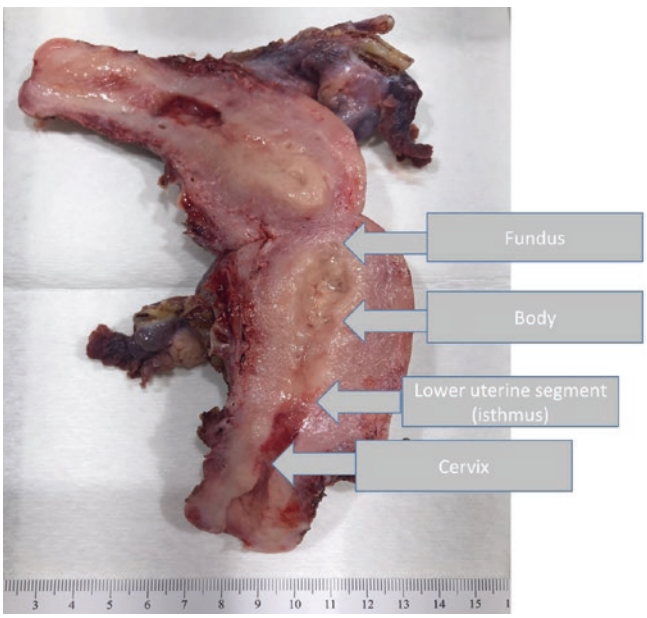


Fig. 1.5 Myometrium in the second trimester. There is more cellularity than in the adult myometrium, and there is significantly less fascicular arrangement of cells

Fig. 1.6 Primary components of the uterus



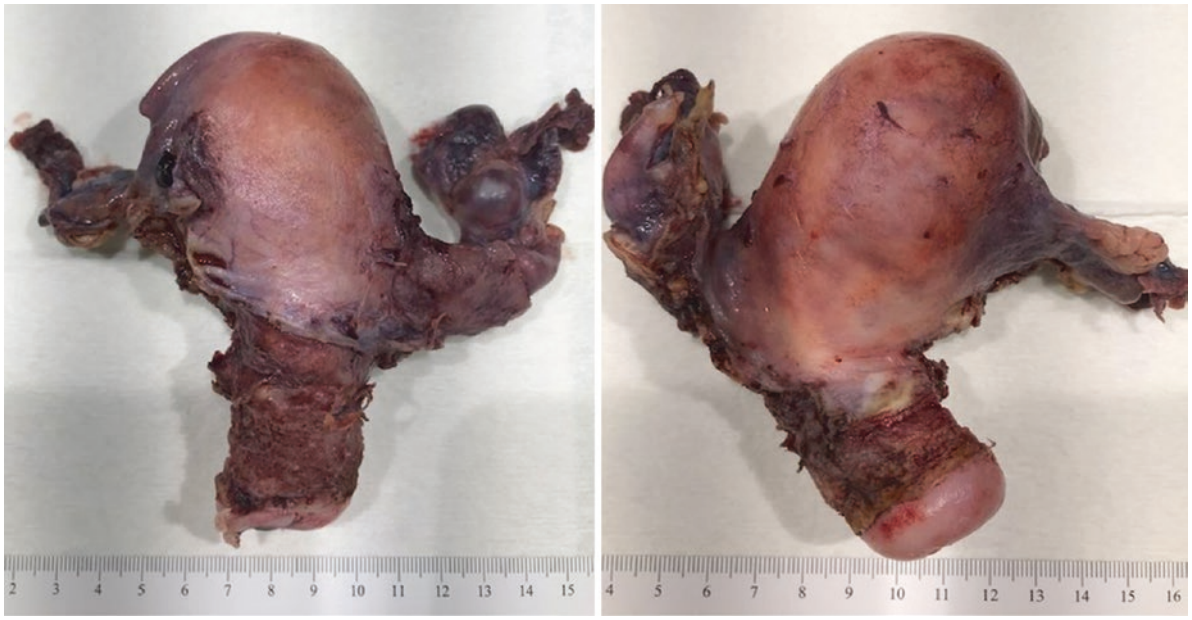


Fig. 1.7 The anterior surface of the uterus (*left*) can be distinguished from the posterior surface (*right*) based on the fact that the anterior surface has a larger area that is devoid of peritoneal lining than the posterior, in its lower component. Additionally, the stump of the round ligament is anteriorly directed

1.2 Uterine Vasculature

The immediate arterial supply of the uterus comprises the right and left uterine arteries, which are subsidiaries of the internal iliac arteries [5, 6]. At the level of the uterine isthmus, the uterine artery on each side bifurcates into two branches, whose subsidiaries include the circumferentially arranged arcuate arteries, their myometrium-penetrating branches (radial arteries), basal branches of radial arteries, and ultimately, the spiral arterioles that terminate in the endometrium (Figs. 1.8, 1.9, 1.10, 1.11, and 1.12). Spiral arteries are hormone-sensitive, and their pericytes have been shown to be estrogen- and progesterone-receptor positive. The venous drainage of the uterus is largely comparable.

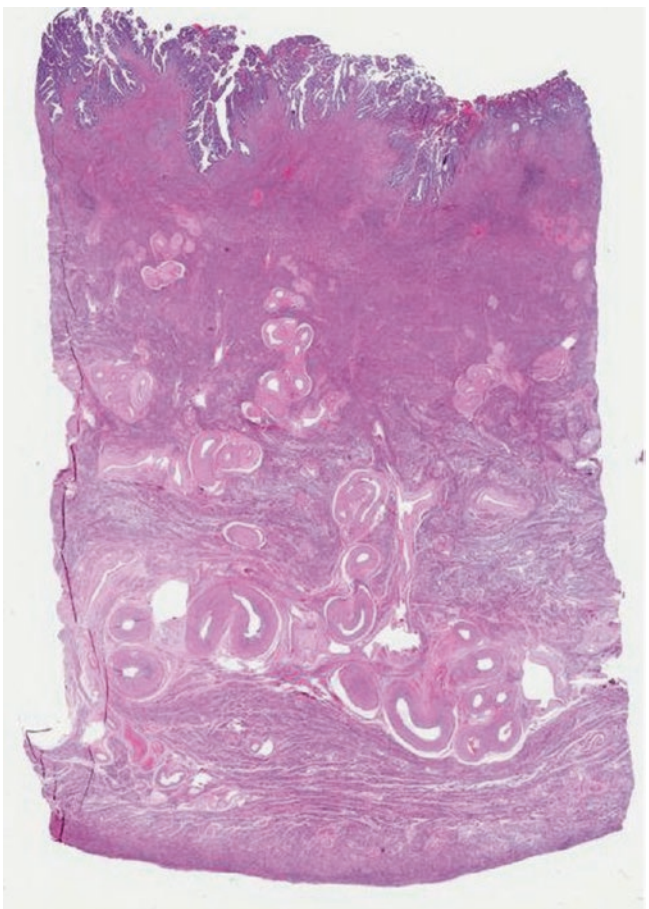


Fig. 1.8 Uterine arteries. Thick-walled vessels of the outer myometrium include the lateral perforating branches of the uterine artery, from which branch the arcuate artery and then the radial arteries. These arteries not infrequently show atherosclerosis and calcification

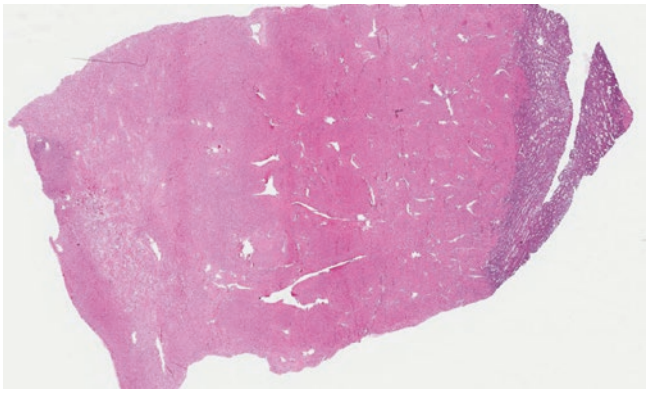


Fig. 1.9 Uterine arteries. Comparing this specimen to Fig. 1.8 highlights the fact the relative thickness and prominence of myometrial vessels may vary significantly between patients

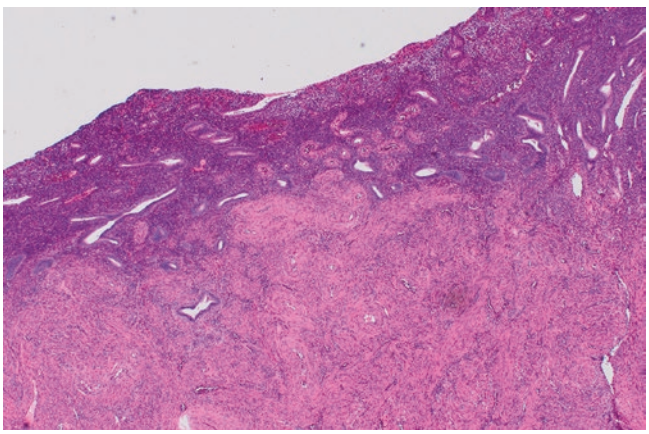


Fig. 1.10 Uterine arteries. Arteries at the endometrial basalis and at the myometrial/endometrial interface may also be prominent and notably clustered. These are basal branches of the radial arteries

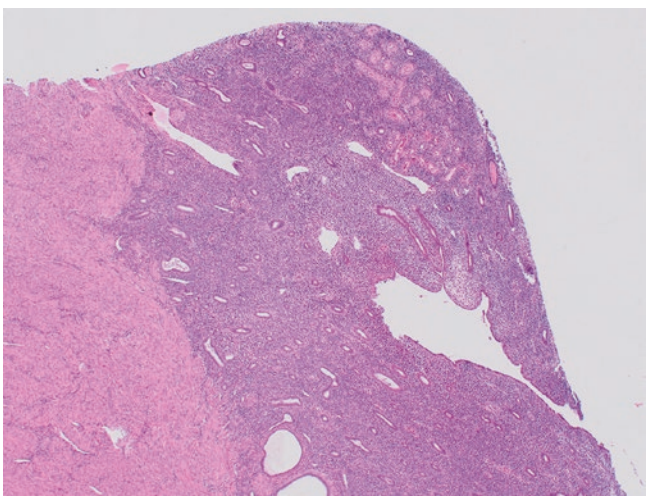


Fig. 1.11 Uterine arteries. Arterioles may occasionally be clustered in the endometrial functionalis; this is a clinically insignificant variation

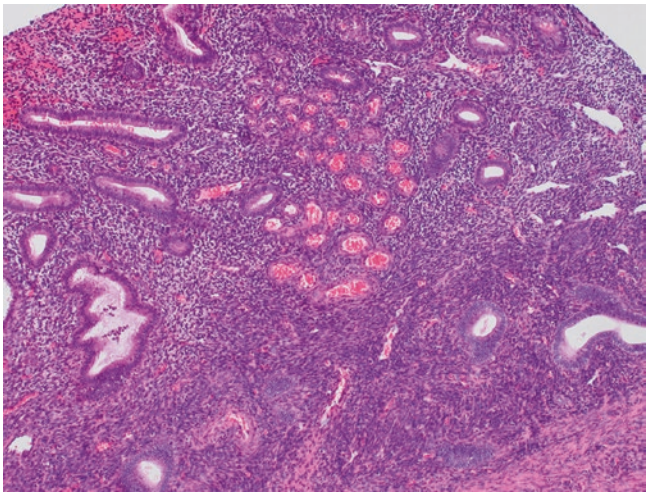


Fig. 1.12 Uterine arteries. Clustered arterioles in the functionalis at high magnification

1.3 Inflammatory Cells of the Endometrium

Leukocytes represent about 10–25% of all endometrial cells, and they vary in number and distribution during the menstrual cycle [7–9] (Figs. 1.13, 1.14, 1.15, 1.16, 1.17, 1.18, 1.19, 1.20, 1.21, 1.22, 1.23, 1.24, 1.25, 1.26, 1.27, 1.28, 1.29, 1.30, 1.31, 1.32, 1.33, 1.34, and 1.35). Table 1.1 summarizes the full distribution of inflammatory cells that may be encountered in the endometrium [8, 9]. Scattered lymphoid aggregates are essentially a normal finding, typically present in the stratum basalis (Fig. 1.32). However, the presence of large numbers of lymphocytic aggregates has been associated with chronic endometritis. There is some evidence that in the setting of chronic endometritis, there is a change in the distribution and ratio of lymphocytic subpopulations. Neutrophils are commonly present when the menstrual phase is well developed, typically around day 2 of the cycle [9, 10] (Fig. 1.35). Plasma cells may be associated with breakdown and menstruation, but may be pathologic when seen in significant populations outside of these settings.

Table 1.1 Relative distribution of inflammatory cells in the functional endometrium at three specific points of the normal menstrual cycle

Cell type	Proliferative phase (days 10–12)	Secretory phase (days 22–23)	Menstrual phase (days 26–28)	Percentage of total endometrial cells at menses
Macrophages	+	++	+++	6–15%
Eosinophils	–	–	++	3–5%
Neutrophils	–	–	+++	6–15%
Mast cells	++	++	++	3–5%
T lymphocytes	+	+	+	1–2%
B lymphocytes	+/–	+/–	+	–
NK cells/granulated lymphocytes	–	+/++	+++	5–6%

Adapted from Salamonsen and Lathbury [8]; *with permission*
NK Natural killer

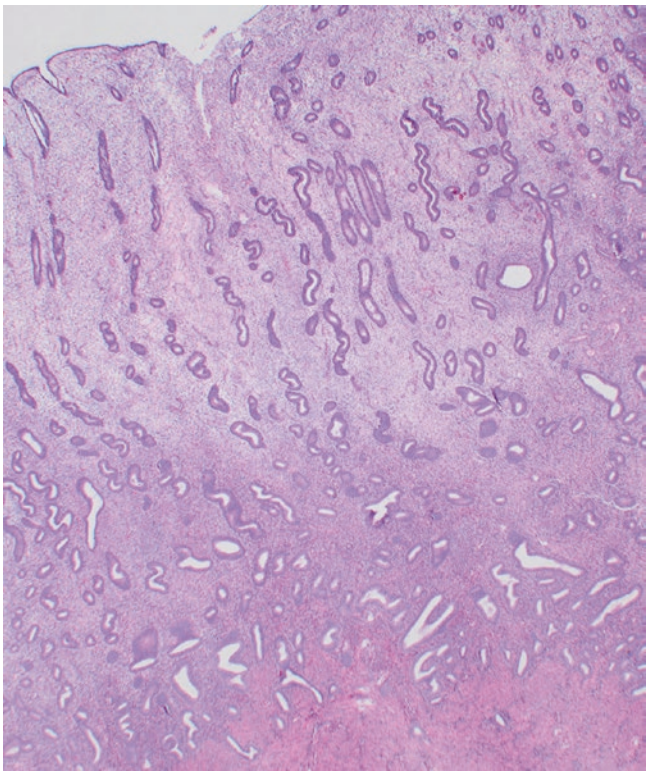


Fig. 1.13 The endometrium is composed of a functional layer (stratum functionalis) and a basal layer (stratum basalis). The functional layer is generally of greater volume than the basal layer, especially in cycling, premenopausal patients. The functional layer shows significantly greater sensitivity to endogenous and exogenous hormones than the basal layer

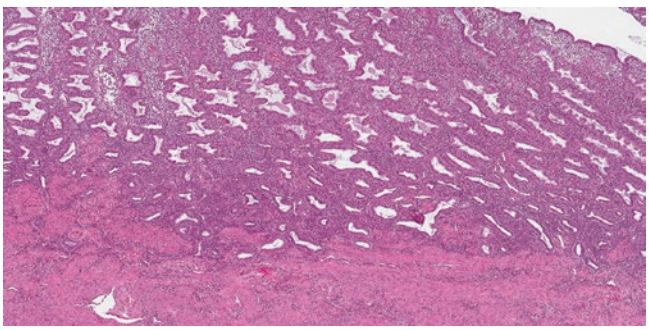


Fig. 1.14 The stratum functionalis in the secretory phase can be classified into a superficial compact layer (stratum compactum) and a deep spongy layer (stratum spongiosum), but in the early and mid parts of the secretory phase, as shown here, the stratum compactum is not apparent

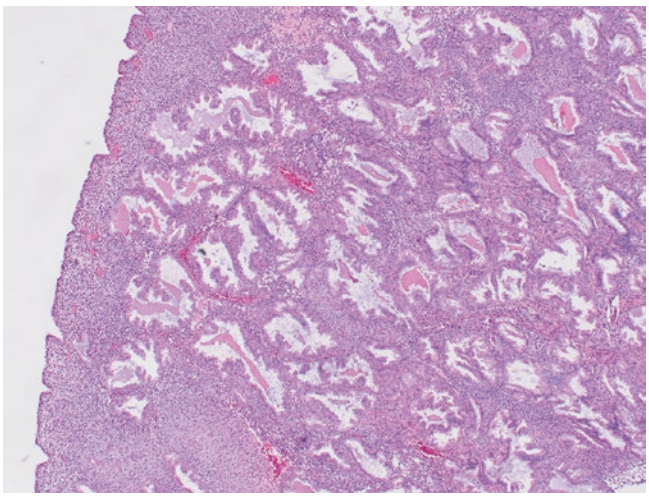


Fig. 1.15 The stratum compactum is the sub-surface epithelial zone that has the appearance of comprising mostly confluent predecidualization. The stratum spongiosum is the deeper zone of serrated glands. The stratum compactum/spongiosum layering is seen in the late secretory phase

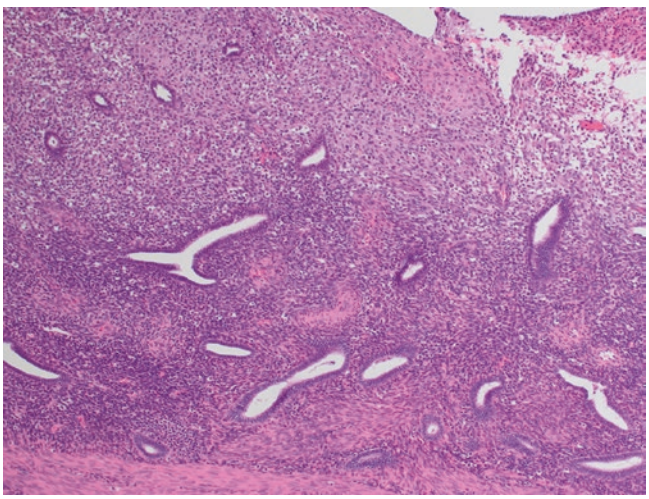


Fig. 1.16 The stratum basalis in a patient who has been treated with exogenous progestins. Even in this setting, the stratum basalis frequently shows less hormonal responsiveness than the stratum functionalis. In the second half of gestation, however, or after prolonged treatment with progestins, the stratum basalis may show alterations consistent with hormone responsiveness, including complete stroma precidualization/decidualization