SPRINGER
REFERENCE

ROBERT J. KURMAN
LORA HEDRICK ELLENSON
BRIGITTE M. RONNETT
EDITORS

Blaustein's Pathology of the Female Genital Tract

Seventh Edition

Springer

Blaustein's Pathology of the Female Genital Tract

Robert J. Kurman • Lora Hedrick Ellenson
Brigitte M. Ronnett
Editors

Blaustein's Pathology of the Female Genital Tract

Seventh Edition

With 1479 Figures and 121 Tables

Springer

Editors
Robert J. Kurman
Department of Gynecology
Obstetrics, Pathology and Oncology
Division of Gynecologic Pathology
Johns Hopkins University
School of Medicine
Baltimore, MD, USA

Lora Hedrick Ellenson
Department of Pathology and Laboratory
Medicine
Division of Gynecologic Pathology
Weill Cornell Medical College and New
York Presbyterian Hospital
New York, NY, USA

Brigitte M. Ronnett
Department of Pathology
Division of Gynecologic Pathology
Johns Hopkins University
School of Medicine
Baltimore, MD, USA

ISBN 978-3-319-46333-9 ISBN 978-3-319-46334-6 (eBook)
ISBN 978-3-319-46335-3 (print and electronic bundle)
https://doi.org/10.1007/978-3-319-46334-6

Library of Congress Control Number: 2018963748

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

Dedication by Dr. Kurman:
To Carole C. Kurman for her constant support and encouragement throughout my career.

Dedication by Dr. Ellenson:
With immeasurable gratitude to Richard, Thomas, and Taite for providing endless joy, support, and inspiration.

Dedication by Dr. Ronnett:
To Lisa, for her unwavering support and unconditional love, and in appreciation of the Johns Hopkins Gynecologic Pathology fellows—past, present, and future—for their invaluable role in our clinical service, which enables our academic pursuits.

Dedication by the editorial team:
We are indebted to our coauthors for their contributions to the current and prior editions, as well as to our fellows and residents, all of whom have made this project possible.

Preface

In science, technological innovation leads to progress. The application of the microscope, most notably the contributions of Virchow, introduced the theory of cellular pathology which led him to propose that cancer developed from otherwise normal cells. Similarly, the application of microscopic analysis to gynecologic tumors by Cullen revolutionized our understanding of gynecologic disease. Today the explosion in the fields of molecular biology and bioinformatics has provided novel information that once again is transforming the field of pathology. The arc of progress in gynecologic pathology can be appreciated by comparing the contents of the first edition of *Blaustein's Pathology of the Female Genital Tract* which appeared in 1977 to this current edition. In the first edition, the etiology of cervical cancer was linked to herpes simplex virus-2 (HSV-2) based on seroepidemiologic studies and electron micrographs showing HSV-2 capsids in cervical carcinoma cells. The role of unopposed estrogenic stimulation in the development of endometrial carcinoma was described but still debated, and carcinoma of the endometrium was classified as endometrial adenocarcinoma, adenoacanthoma, adenosquamous carcinoma, and squamous carcinoma. In the fallopian tube chapter, one half a page was devoted to carcinoma in situ (intraepithelial carcinoma). Gestational trophoblastic disease was classified into three categories, hydatidiform mole, invasive mole, and choriocarcinoma. We now recognize that cervical cancer is due to human papillomavirus (HPV), and with universal adoption of vaccination for HPV, cervical cancer can conceivably be eradicated in the future. The histopathologic classification of endometrial cancer has been expanded, and the most recent next-generation sequencing studies suggest that it can be classified into four major molecular subtypes (Kandoth et al. 2013). Our entire concept of epithelial ovarian carcinoma has undergone a paradigm shift with attention now directed at the fallopian tube as the site of origin. A recent study that incorporates assays for mutations on liquid cervical samples and an assay for aneuploidy on circulating tumor DNA from plasma was shown to have high sensitivity and specificity for the detection of ovarian and endometrial cancer, demonstrating the potential for diagnosing ovarian and endometrial cancer based entirely on molecular genetic studies, at an early stage, when these carcinomas are more likely to be cured. Clearly, a lot has changed in the ensuing years. We think how simplistic and naive our understanding of gynecologic disease was 40 years ago, but future generations, 40 years from now, will look back at this edition and have the same reaction. Assessing where we are today and speculating on what the future may hold in store, we

recognize that pathology stands at a crossroads as morphologic diagnosis gives way to molecular diagnosis. Given the pace of personalized medicine, it is possible that in the not too distant future classification systems may become obsolete as each individual's tumor will be classified based on its unique molecular alterations. To guide this transition, it is critical that traditional morphologic analysis be carefully correlated with immunohistochemical and molecular biologic findings. This is one of the major contributions that the current edition of the Blaustein text aims to fulfill. In the preface of the first edition, Ancel Blaustein stated that "the text is written for obstetricians, gynecologists, pathologists and for residents training in these disciplines." We recognize that this goal has been more than fulfilled as countless numbers of pathologists, gynecologists, and a host of physicians in other specialties have turned to this textbook to provide the most up-to-date information on the nature of gynecologic disease including discussion of diagnosis and treatment. This edition carries on this long tradition. The present edition has been rewritten to include advances in the field which, as noted earlier, are now largely based on the contributions of molecular biology. Since the last edition, the WHO Classification has been revised, and the classification systems used herein are those proposed by the WHO. Dr. Blaustein also had the prescience to realize that even in 1977 a comprehensive text necessitated multiple authors stating that "the expansion of information in the field of gynecologic pathology renders single authorship obsolete." Accordingly, that first edition was the first textbook in pathology to have multiple contributors. With the passage of time, contributors have passed on or retired, and we have therefore recruited young, up-and-coming experts to replace previous contributors and to reinvigorate the textbook with new ideas and concepts. In that vein Dr. Kurman, having edited this textbook beginning with the third edition, will be stepping down and turning over the editorship to Drs. Ellenson and Ronnett who will succeed him and carry on the long tradition of this text as an invaluable educational resource in the field of obstetrics and gynecology.

Robert J. Kurman, M.D.
Lora Hedrick Ellenson, M.D.
Brigitte M. Ronnett, M.D.

References

Kandoth C, Schultz N et al (2013) Integrated genomic characterization of endometrial carcinoma. Nature 497(7447):67–73

Wang Y, Li L, Douville C et al (2018) Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers. Sci Transl Med 10:eaap8793, 1–9

Contents

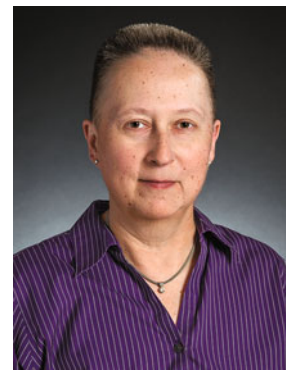
About the Editors

Dr. Robert J. Kurman, **M.D.**, is the Emeritus Richard W. TeLinde Distinguished Professor of Gynecologic Pathology at the Johns Hopkins University School of Medicine and former Director of the Division of Gynecologic Pathology at the Johns Hopkins Hospital where his career was devoted to diagnosis, research, and teaching in the field of gynecologic pathology. His research activities began in the early 1970s with studies of germ cell tumors of the ovary and testis and gestational trophoblastic disease at which time he pioneered the application of immunohistochemistry (IHC) on formalin-fixed, paraffin-embedded tissue. These studies were among the first describing how IHC could be applied to surgical pathology. During this time, he also undertook studies on the relationship of endometrial hyperplasia to carcinoma which led to the development of a classification system of endometrial hyperplasia that was later adopted by the World Health Organization. In the late 1970s and 1980s, his work on establishing the link between HPV and cervical cancer played a role in the application of molecular testing for HPV as a screening tool. This also was instrumental in the development of "The Bethesda System (TBS) for Reporting Cervical/Vaginal Cytologic Diagnoses" that replaced the previous Papanicolaou classification system and is now the standard cytology

classification system in the USA and abroad. He has also been a Consultant for Merck in their clinical HPV vaccine trials. In the last 15 years, he has focused on elucidating the pathogenesis of epithelial ovarian cancer. By collaborating not only with other pathologists but also with molecular biologists and epidemiologists, he has demonstrated the value of a multimodal approach to ovarian cancer research. His vision has led to the proposal of a new disease model, which synthesizes clinical observations and pathobiological mechanisms and validates conceptual hypotheses with molecular data, thereby bringing new insights to the field. For example, based on morphologic and molecular genetic studies, a dualistic model of ovarian carcinogenesis was developed, which has now become widely accepted in the field. In addition, the studies implicating a precursor lesion in the fallopian tube as the origin of many so-called ovarian carcinomas have dramatically changed our thinking on this subject, with important implications for ovarian cancer screening and prevention. His research has resulted in the publication of nearly 300 original peer-reviewed papers and over 150 review articles and book chapters. Dr. Kurman's influence extends well beyond these research efforts. He has recruited and mentored pathologists and researchers who have become distinguished gynecologic pathologists. Pathologists know him as an author and editor through his significant educational publications, including *Blaustein's Pathology of the Female Genital Tract* (third, fourth, fifth, and sixth editions), *Diagnosis of Endometrial Biopsies and Curettings: A Practical Approach* (two editions), the AFIP Fascicles on *Tumors of the Cervix, Vagina, and Vulva* (third and fourth series) and *Tumors of the Uterine Corpus and Gestational Trophoblastic Disease* (third series), and the 2014 *World Health Organization Classification of Tumours of the Female Reproductive Organs*. He is sought after as a lecturer worldwide and has contributed to the advancement of the field through his leadership in professional societies, including being President of the International Society of Gynecologic Pathologists, participation in international committees, and membership on editorial boards of numerous journals. In recognition of his scholarship and leadership activities, he was elected as an Honorary Fellow of the Royal College of Pathologists and the Austrian Society of Pathologists.

Lora Hedrick Ellenson, **M.D.**, is Professor and Director of Gynecologic Pathology in the Department of Pathology and Laboratory Medicine at Weill Cornell Medical College in New York City. Her undergraduate work was done at the University of California, Berkeley, followed by medical school at Stanford University School of Medicine and residency training at the Johns

Hopkins Medical Institutions. Upon completing the Anatomic Pathology program, she joined the laboratory of Drs. Bert Vogelstein and Ken Kinzler as a postdoctoral fellow. She simultaneously trained as a Gynecologic Pathologist with Dr. Robert Kurman. Following her initial work studying the molecular biology of colon cancer, at the request of Dr. Kurman, she joined the Department of Pathology in the Division of Gynecologic Pathology where she established an independent research program to study the molecular genetics of endometrial carcinoma. Dr. Ellenson's laboratory was one of the first to document the high frequency of *TP53* mutations in uterine serous carcinoma and microsatellite instability and *PTEN* mutations in sporadic endometrioid carcinoma. In 1998, after becoming an Associate Professor at Johns Hopkins, she moved to Weill Cornell Medical College to oversee the Division of Gynecologic Pathology. Reflecting her expansive interests, Dr. Ellenson has, throughout her career, maintained an NIH-funded laboratory and simultaneously practiced diagnostic gynecological pathology. Since 2001, she has been an Associate Editor for *The American Journal of Pathology*. She has also been on the Editorial Committee for *Annual Reviews of Pathology: Mechanisms of Disease* for over 10 years. Dr. Ellenson has contributed chapters on the female genital tract for the last three editions of *Robbins and Cotran Pathologic Basis of Disease* and more recently for *Basic Pathology*. More recently, she became Editor in Chief of the *International Journal of Gynecological Pathology* and is on the editorial committee for the next edition of the WHO Classification of Tumours of Female Reproductive Organs.



Brigitte M. Ronnett, **M.D.**, is Professor of Pathology and Gynecology and Obstetrics at the Johns Hopkins Medical Institutions. She graduated from Northwestern University and received her medical degree from the University of Chicago Pritzker School of Medicine. She completed residency training in pathology at the Johns Hopkins Hospital, a surgical pathology fellowship at Memorial Sloan-Kettering Cancer Center, and both surgical pathology and gynecologic pathology fellowships at the Johns Hopkins Hospital. She has been a member of the Division of Gynecologic Pathology at Johns Hopkins since 1995. Her clinical efforts are focused on a large gynecologic pathology consultation practice. Her research efforts have focused on ovarian mucinous tumors, uterine cervical and endometrial pathology, and hydatidiform moles.

Contributors

Rebecca N. Baergen Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY, USA

Kathleen R. Cho Department of Pathology, University of Michigan Medical School, Ann Arbor, MI, USA

Philip B. Clement Department of Pathology, Vancouver General Hospital, Vancouver, BC, Canada

Judith A. Ferry James Homer Wright Pathology Laboratories of the Massachusetts General Hospital, Department of Pathology, Harvard Medical School, Boston, MA, USA

John F. Fetsch Soft Tissue Pathology, The Joint Pathology Center, Silver Spring, MD, USA

Deborah J. Gersell Department of Laboratory Medicine, St. John's Mercy Medical Center, St. Louis, MO, USA

Lora Hedrick Ellenson Department of Pathology and Laboratory Medicine, Division of Gynecologic Pathology, Weill Cornell Medical College and New York Presbyterian Hospital, New York, NY, USA

Julie A. Irving Department of Laboratory Medicine, Pathology, and Medical Genetics, Royal Jubilee Hospital, Victoria, BC, Canada

Frederick T. Kraus Perinatal Biology Laboratory, Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, MO, USA

Robert J. Kurman Department of Gynecology, Obstetrics, Pathology and Oncology, Division of Gynecologic Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

William B. Laskin Department of Pathology, Yale Surgical Pathology, Yale School of Medicine, New Haven, CT, USA

Ricardo R. Lastra Department of Pathology, University of Chicago, Chicago, IL, USA

Melinda F. Lerwill Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Kruti P. Maniar Department of Pathology, Division of Surgical Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Michael Mazur Department of Pathology, SUNY Upstate Medical University, Syracuse, NY, USA

W. Glenn McCluggage Department of Pathology, Royal Group of Hospitals Trust, Belfast, UK

Marisa R. Nucci Division of Women's and Perinatal Pathology, Department of Pathology, Brigham Women's Hospital, Boston, MA, USA

Esther Oliva Massachusetts General Hospital, Boston, MA, USA

Department of Pathology, Harvard Medical School, Boston, MA, USA

Edyta C. Pirog Department of Pathology, Weill Cornell, Medical College and New York Presbyterian Hospital, New York, NY, USA

Brigitte M. Ronnett Department of Pathology, Division of Gynecologic Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Demaretta S. Rush Department of Pathology, University of Arizona College of Medicine, Tucson, AZ, USA

Lauren E. Schwartz Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Jeffrey D. Seidman Center for Devices and Radiological Health, Office of In Vitro Diagnostics and Radiological Health, Food and Drug Administration, Silver Spring, MD, USA

Ie-Ming Shih Gynecologic Pathology Laboratory in the Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Robert A. Soslow Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Department of Pathology and Laboratory Medicine, Weill Cornell Medical College and New York Presbyterian Hospital, New York, NY, USA

Paul N. Staats Department of Pathology, University of Maryland School of Medicine, Baltimore, MD, USA

Edyta C. Pirog has retired.

Russell Vang Department of Pathology, Division of Gynecologic Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA

Edward J. Wilkinson Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, Gainesville, FL, USA

Thomas C. Wright Department of Pathology and Cell Biology, Columbia University, New York, NY, USA

Robert H. Young Anatomic Pathology, James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Richard J. Zaino Hershey, PA, USA

Charles J. Zaloudek Department of Pathology, University of California, San Francisco, San Francisco, CA, USA

Benign Diseases of the Vulva

1

Demaretta S. Rush and Edward J. Wilkinson

Contents

D. S. Rush
Department of Pathology, University of Arizona College of Medicine, Tucson, AZ, USA
e-mail: rushd@pathology.arizona.edu

E. J. Wilkinson (✉)
Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, Gainesville, FL, USA
e-mail: wilkinso@pathology.ufl.edu

R. J. Kurman et al. (eds.), *Blaustein's Pathology of the Female Genital Tract*,
https://doi.org/10.1007/978-3-319-46334-6_1

Anatomy

The external female genitalia include the mons pubis, labia majora and minora, clitoris, and vestibule. The mons is the portion of hair-bearing skin and associated subcutaneous tissue overlying the pubic symphysis. Inferior to the pubis, the hair-bearing skin of the mons divides into two folds, the labia majora, which join posteriorly at the perineal body, just anterior to the anus. Medial to the labia majora are a second set of folds, the labia minora, each of which divides at the anterior end into two sets of smaller folds. The superior folds fuse in the midline anterior to the clitoris, forming the prepuce, or clitoral hood, and the inferior folds fuse in the midline posterior to the clitoris, forming the frenulum. Posteriorly, the labia minora fuse without further divisions, at the fourchette, posterior to the introitus and anterior to the perineal body. The clitoris consists of a bundle of erectile tissue situated in the midline, with just the tip, or glans, visible between the prepuce and frenulum. Beneath the surface is the body of the clitoris which branches at the base into two crurae running along the pubic rami in the deep soft tissue. The vestibule is a roughly diamond-shaped area bounded anteriorly by the frenulum of the clitoris, laterally by the medial edges of the labia minora, and posteriorly by the fourchette. Posterior to the frenulum on the vestibule is the urethral orifice, and posterior to that lies the vaginal opening, bounded by the hymen or remnants thereof. The external anatomy is illustrated in Fig. 1.

Histologically, the hair-bearing skin of the mons is similar to the nongenital skin of the rest of the body, consisting of keratinizing squamous epithelium with all of the usual adnexal skin structures, including hair follicles, sebaceous glands, eccrine sweat glands, and sensory receptors. The subcutaneous tissue of the mons is predominantly adipose tissue. The composition of the labia majora is nearly identical, but with an additional component of smooth muscle in the subcutaneous tissue and apocrine sweat glands deep to the epithelium. On the medial portion of the labia majora, the skin becomes hairless, and there is a corresponding absence of hair follicles, as well as an absence of sweat glands, although sebaceous glands remain and may be rather prominent in appearance, forming slightly elevated, pale areas known as Fordyce spots. The epithelium becomes thinner and keratinization decreases on the medial surface of the labia majora as well. The labia minora are composed of connective tissue rich in elastic fibers and blood vessels but without adipose tissue. The mucosa of the labia minora is similar to the medial portion of the labia majora, with which it is continuous, with sebaceous glands disappearing toward the medial side. The theoretical line of Hart, which runs along the medial edge of the labia minora, marks the junction between the keratinizing epithelium of the labia minora and the nonkeratinizing squamous mucosal lining of the vestibule. The mucosa of the vestibule is glycogenated in women of reproductive age, or under estrogen influence, and resembles vaginal mucosa. This epithelium merges with the transitional epithelium at the urethral meatus and with the duct openings of various submucosal glands.

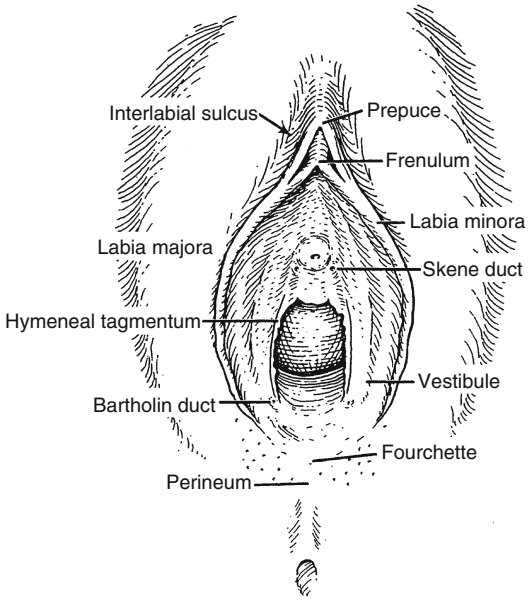


Fig. 1 Anatomy of the vulva. The vestibule is the diamond-shaped area between the medial edges of the labia minora, extending from the frenulum to the fourchette, and containing the urethral and vaginal openings

The glandular structures of the vulva are not normally visible on external exam, or even on careful dissection, and many can only be seen microscopically unless enlarged by disease. Aside from the sweat glands in the hair-bearing portions of the vulva, which are no different from those elsewhere on the skin, there are a number of glandular structures specific to the vulvar area. Situated in the interlabial sulcus, surrounding the entire labia minora and clitoris, and on the perineum and surrounding the anus, are specialized apocrine glands, the anogenital mammary-like glands. These glands have a simple columnar epithelium with apical snouts and myoepithelium surrounding the glandular epithelium (van der Putte 1991). They may be located as far as 3.9 mm from the surface (Konstantinova et al. 2017a) and have long and wide coiled ducts that open to the surface. The paired Skene's glands, homologues of the male prostate, are composed of pseudostratified mucus-secreting columnar epithelium and open to the external surface on both sides of the urethral meatus and along the posterior and lateral aspects of the urethra itself.

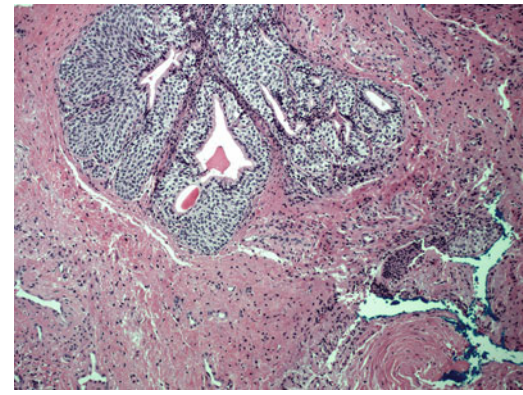


Fig. 2 Skene gland. The gland is lined by a mixture of urothelium and mucin-secreting columnar epithelium

The ducts are lined by transitional epithelium (Fig. 2). The Bartholin glands are bilateral racemose, tubuloalveolar glands, with acini composed of simple, columnar, mucus-secreting epithelium (Fig. 3). The Bartholin duct, approximately 2.5 cm in length, has three types of epithelial linings depending on the location within the duct. It is lined proximally by mucus-secreting epithelium, distally by transitional epithelium, and, at its exit, just external to the hymen ring of the vestibule posterolaterally, by squamous epithelium. The minor vestibular glands ring the vestibule and extend from the frenulum on both sides of the urethral meatus around the external base of the hymenal ring to the fourchette, lying within 1–2.5 mm of the superficial epithelium and communicating with the vestibular surface. They are composed of acini lined by simple columnar mucus-secreting epithelium.

The major blood supply to the vulva is provided via the anterior and posterior labial branches of the superficial and deep external pudendal arteries, which branch from the femoral artery, and the internal pudendal arteries, which branch from the internal iliac arteries. The clitoris, including the crura and corpora cavernosa, is supplied separately by the deep arteries of the clitoris, whereas the anterior vaginal artery supplies blood flow to the vestibule and the Bartholin glands. The venous return parallels the arterial supply. The nerve supply to the vulva includes sensory nerves,

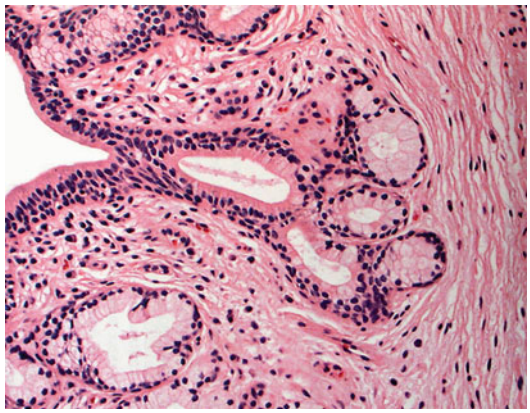


Fig. 3 Bartholin gland and duct. The glandular acini are composed of simple mucin-secreting columnar epithelium which merges with the transitional epithelium lining the duct

special receptors, and autonomic nerves to the vessels and various glands. The major nerves of the vulva derive from the anterior (ilioinguinal) and posterior (pudendal) labial nerves. The clitoris is innervated by the dorsal nerve of the clitoris and the cavernous nerves of the clitoris, which also supply the vestibule.

The entire vulva, with the exception of the clitoris, drains to the femoral and inguinal lymph nodes. Delicate intercommunicating lymphatic vessels extend to the labia minora, clitoral prepuce, and vestibule, bypassing the clitoris. The lymphatic bed of the labia majora drains in an anterosuperior direction toward the mons, joining the lymphatic vessels from the labia minora and prepuce, and then into the ipsilateral inguinal and femoral nodes. Some contralateral flow also may occur into the superior medial nodes of the femoral group. The superficial inguinal lymph nodes, consisting of 8–10 nodes on each side, divided into a superior oblique and an inferior ventral group, are the major nodes that drain the vulva and therefore are included in a radical vulvectomy. The superior oblique group is found about the Poupart ligament, and the inferior ventral group lies above the junction of the saphenous vein and fascia lata. Lymphatic drainage from the clitoris and midline perineum proceeds bilaterally in more than 67% of cases and may bypass the superficial nodes. A second minor lymphatic pathway from the glans clitoris joins the lymphatics of the urethra, traverses the urogenital diaphragm, and merges with the lymphatic plexus on the anterior surface of the bladder. From there, drainage is into the internal iliac, obturator, and external iliac nodes.

Developmental Abnormalities

Congenital

Congenital anomalies of the vulva may include absence, hypoplasia, hyperplasia, or dupilication of various portions of the anatomy. Congenital absence of the clitoris and external genitalia has been described. In Müllerian agenesis, the external genitalia is largely intact, but the hymen and vagina are absent, usually represented only by a depression in the vestibular area. True hypoplasia of the labia minora occurs infrequently and may be a sign of defective steroidogenesis. Hypertrophy of the labia minora is more common, usually becoming more evident at puberty, and is defined as a measurement of more than 4 cm from the base to the outer edge (Margesson 2006). Clitoral enlargement may be seen in newborns with adrenogenital syndrome or who have been exposed in utero to exogenous maternal androgen therapy, as well as in hermaphroditism and, rarely, with lipodystrophy (Ridley and Neill 1999). Labial fusion may also may be present with intersex disorders, although slight fusion of the labia minora may be seen in infants without apparent cause and typically responds to topical estrogen cream. Urethral anomalies may result in aberrant locations of the urethral opening in the vagina or adjacent to the hymen rather than in the upper portion of the vestibule (Kaufman 1994). Duplication of the vulva is extremely rare and usually is associated with duplication of the internal Müllerian system and rectum as well.

Acquired

Many vulvar conditions may result in altered anatomy later in life. In some cases, labial hypertrophy

may develop over time in association with chronic irritation, as from indwelling catheters. Labial fusion may also be an acquired abnormality, secondary to adhesions and scarring in the course of lichen sclerosus (LS), lichen planus (LP), or other inflammatory conditions, or female genital mutilation procedures. Female genital mutilation is practiced in parts of Africa, Asia, and the Middle East, and affected patients are increasingly encountered in Western medical practice, where they present with a variety of alterations to the vulvar anatomy which may be complex (Abdul-Cadir et al. 2016). These procedures involve removal of various portions of the vulva and may include reapproximations of the cut margins to partially or completely obscure the vaginal opening. In addition to destroying the normal anatomy, female genital mutilation may lead to complications which can further distort the vulva. Epidermal inclusion cysts of the vulva seem to be a particularly common complication and often present many years after the procedure as large, frequently pedunculated masses which may measure up to 7 cm and may be mistaken for clitoral enlargement due to hormonal factors or neoplasia (Riszk et al. 2007, Osarumwense 2010, Asante et al. 2010). A variety of tumors including granular cell tumors, hemangiomas, and vascular, neural, and smooth muscle tumors may also cause acquired clitoral enlargement.

Infectious Conditions

In developed nations, the most prevalent infections of the vulva are sexually transmitted viral diseases due to human papillomavirus (HPV), herpes simplex virus (HSV), and molluscum contagiousum and syphilis, a bacterial disease. Many other pathogens, however, not all of them sexually transmitted, may involve the vulva. Most vulvar infections are readily diagnosed on clinical grounds or by ancillary testing. Biopsies of these conditions are generally performed only when the presentation is atypical or the diagnosis is otherwise in doubt. Although the histopathologic findings are frequently nonspecific, there may be features at least suggestive of a particular etiologic agent, which can guide the selection of additional testing to establish a definitive diagnosis. A summary of the principal vulvar infections presented in this chapter is provided in Table 1.

Bacterial

Syphilis

For many years, the rates of syphilis infection had been declining in the West, reaching a historic low in 2000, but began to climb again, particularly in the human immunodeficiency virus (HIV)-positive population (Cohen et al. 2013; Hope-Rapp et al. 2010) and in pregnant women, in subsequent years. The disease is caused by *Treponema pallidum*, a spirochete which does not stain with Gram stain and which cannot be cultured, making it particularly important to be aware of the characteristic clinical and microscopic features.

Clinical Features

The disease manifests in phases. A week to 3 months after initial exposure, the primary lesion, or chancre, appears as a papule which develops into a painless, indurated, shallow, clean-based ulcer with raised edges. Chancres are usually single but may be multiple, especially in HIV-positive patients (Cohen et al. 2013). They may occur on inconspicuous surfaces, such as the cervix, anal mucosa, or oropharynx, and it is not uncommon for the primary lesion to go unnoticed and untreated. Typically, the chancre will heal on its own within 2–6 weeks.

The timing of the development of the secondary stage of syphilis is variable but typically manifests 2–8 weeks after the chancre. At this point, the patient may present with a skin rash that often involves mucous membranes as well as the palms of the hands and soles of the feet, as well as with systemic symptoms of fever, headache, pharyngitis, and lymphadenopathy. Secondary syphilis may be accompanied by new painless cutaneous lesions known as condylomata lata and by mucous patches. Condylomata lata appear as elevated papules or plaques with a velvety papillary surface,

Table 1 Summary of significant vulvar infections, their clinical manifestations, and suggested ancillary tests to assist in their diagnosis

Infectious conditions of the vulva			
Diagnosis	Etiologic agent	Clinical manifestation(s)	Ancillary tests
Bacterial			
Syphilis	*Treponema pallidum*	Primary: Chancre (ulcer) Secondary: Condylomata lata (papule)	Dark field examination Immunofluorescence Immunohistochemistry Polymerase chain reaction (PCR) Serology
Granuloma inguinale	*Klebsiella granulomatis*	Ulcer	Culture Warthin-Starry or gram stain ("Donovan bodies")
Lymphogranuloma venereum (LGV)	*Chlamydia trachomatis*, types L1, L2, L3	Ulcer, +/− inguinal lymphadenopathy	Serology Culture PCR
Chancroid	*Haemophilus ducreyi*	Ulcer	Culture PCR Gram or Giemsa stain
Tuberculosis	*Mycobacterium tuberculosis*	Ulcers, swellings, exophytic lesions	Culture Acid-fast stain
Viral			
Condyloma acuminatum	HPV, usually types 6 and 11	Condyloma acuminatum (genital warts)	Not necessary
Herpes	HSV, types 1 and 2	Ulcers, atypical lesions in immunosuppressed patients	Culture PCR Immunohistochemistry
Varicella (vulvar shingles)	Herpes zoster	Unilateral vesicles and ulcers	PCR Immunohistochemistry
Molluscum contagiosum	*Molluscum contagiocsum*		Not necessary
Fungal			
Various	Various	Scaly plaques (most commonly)	Skin scrapings for KOH prep PAS or silver stains Culture
Parasitic			
Various	Various	Various	Usually not necessary

involving the vulva, perianal, and inguinal area and measuring up to 3 cm in diameter (Fig. 4), while mucous patches appear as gray-white erosions on the non-hair-bearing squamous mucosa of the inner labia. Both condylomata lata and mucous patches are heavily populated with spirochetes and are highly infectious.

The tertiary phase of syphilis, which develops after many years of latency, is extremely uncommon today. Its most significant manifestations involve the cardiovascular and central nervous systems, although cutaneous or mucosal granulomatous lesions, or gummas, may also develop in this phase.

Microscopic Findings

The primary chancre is characterized by ulceration of the epithelium with intense acute and chronic submucosal and perivascular inflammation, characterized by the presence of large numbers of plasma cells. Granulomatous inflammation may also be present.

Histologic examination of condylomata lata reveals marked acanthosis and hyperkeratosis, patchy parakeratosis, and superficial intraepithelial microabscesses. Also present is a chronic inflammatory response within the dermis with a perivascular distribution, similar to that in the primary chancre but with a greater

predominance of plasma cells. The arteritis in the lesions of both primary and secondary syphilis may be sufficiently severe to result in obliteration of the smaller vessels. Other patterns of inflammation may also be seen in secondary syphilis, including a psoriasiform pattern, a lichenoid form, and a pustular form, in which the prominence of plasma cells in the inflammatory infiltrate and the endarteritis should raise the suspicion for syphilis (Fig. 5).

Dieterle, Warthin–Starry, or Steiner stains for spirochetes may be of some use to identify the organisms, which are characteristically located at the dermal-epidermal junction and in a perivascular distribution in the superficial dermis, but these stains may be negative even with active infection. Immunohistochemical staining is now available and considerably easier to interpret (Fig. 6), and the organisms may also be identified on dark-field examination of fresh sera from an active lesion, by a fluorescent conjugated antibody technique, which employs a dried smear preparation, and by PCR. These tests are all much more sensitive and specific for detection of the organisms than silver staining techniques but are also more expensive and may not be available in all clinical settings. For confirmation of the diagnosis, serologic tests, which are widely available and may be used in place of or in addition to microscopic examination of clinical samples, are most commonly used. Serology is very sensitive in secondary syphilis but may be falsely negative in primary syphilis, in which case the test may need to be repeated at a later time.

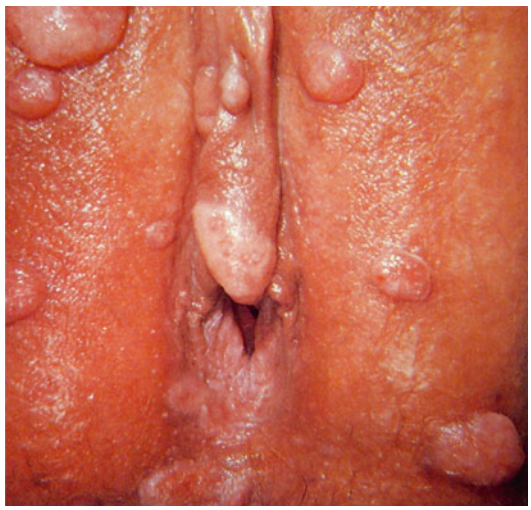


Fig. 4 Condyloma lata. The lesions are exophytic, but with a relatively smooth, uniform surface

Clinical Course and Treatment

Approximately 30% of patients with primary syphilis will undergo spontaneous remission of the disease. Those who are not treated or who do not achieve spontaneous remission may progress to tertiary syphilis, which, if it continues to go untreated, may prove to be fatal in 10% of those afflicted. Penicillin or another appropriate systemic antibiotic is the treatment of choice for all stages of the disease.

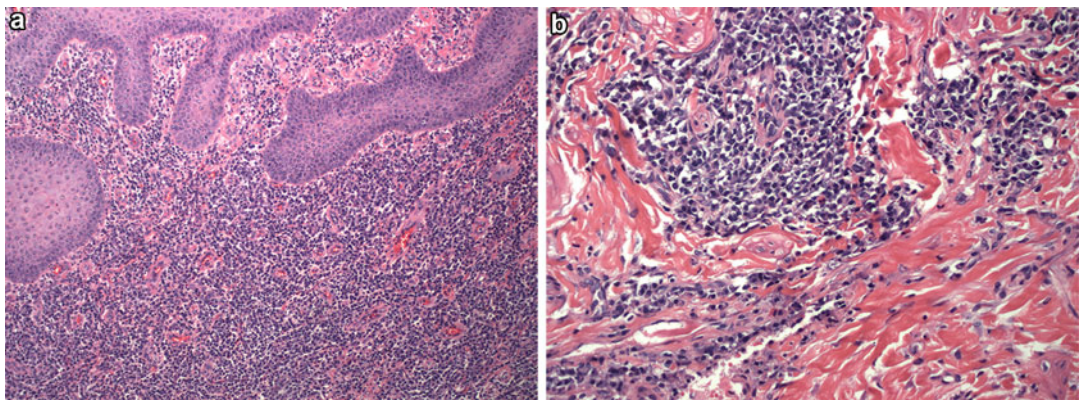


Fig. 5 **(a)** Secondary syphilis. This lesion shows prominent pseudoepitheliomatous hyperplasia overlying a dense dermal inflammatory infiltrate containing abundant plasma cells. **(b)** Deeper in the dermis, the inflammatory infiltrate shows a perivascular distribution

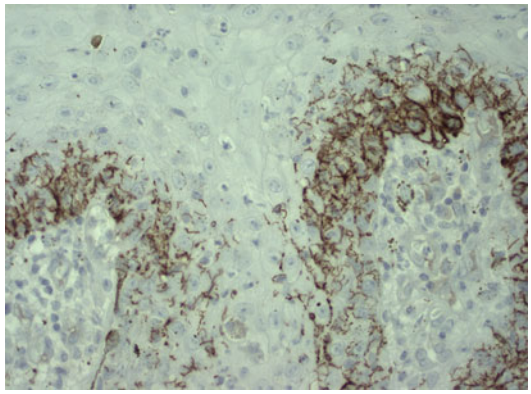


Fig. 6 Immunohistochemical stain for *Treponema pallidum* in the lesion illustrated in Fig. 5. The organisms are concentrated at the dermo-epidermal junction, and the characteristic spiral structure is evident

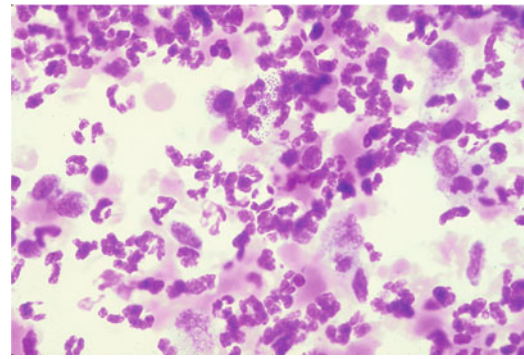


Fig. 7 Granuloma inguinale. Giemsa stain shows numerous intracytoplasmic "Donovan bodies" with a characteristic halo surrounding the organisms

Granuloma Inguinale

Granuloma inguinale, also known as donovanosis or granuloma venereum, is a sexually transmitted disease endemic to Papua New Guinea, South Africa, India, Brazil, and Australia. Occasional local outbreaks of the disease are seen in the West. The disease is caused by a gram-negative, heavily encapsulated rod formerly known as *Calymmatobacterium granulomatis* but recently reclassified as *Klebsiella granulomatis* (O'Farrell and Moi 2016).

Clinical Features

In women, the primary lesions occur on the vulva, vagina, or cervix. The lesions usually appear within 1 week to 1 month of exposure; anal coitus or fecal contamination of the vulva or vagina has been posited as the mode of transmission (Wilkinson and Stone 2008). Four types of lesions have been described: ulcerogranulomatous, hypertrophic, necrotic, and sclerotic/cicatricial, but the typical lesion begins as a papule which develops into an ulcer which then progressively increases in size. Despite its name, granuloma inguinale involves the inguinal region in only 10% of cases (O'Farrell and Moi 2016).

Microscopic Findings

Histologically, the main portion of the lesion consists of granulation tissue associated with an extensive chronic inflammatory cell infiltrate and endarteritis. The ulcer is usually covered with a fibrinous exudate, while the surface epithelium adjacent to the ulcer may show prominent pseudoepitheliomatous hyperplasia. Necrosis and microabscesses may be seen within the epidermis. The granulation tissue is accompanied by a dense mixed inflammatory cell infiltrate, consisting predominantly of plasma cells and mononuclear cells with few lymphocytes, which extends into the dermis.

All of these findings, however, are nonspecific, and the diagnosis cannot be made with certainty without identification of the offending organisms. These show a characteristic bipolar staining pattern, likened to a "safety-pin," on Warthin–Starry stain or Giemsa stain and are referred to as "Donovan bodies." They are found within the cytoplasm of large vacuolated histiocytes in the lesion, as well as intracellularly (Fig. 7). Organisms may also be identified by preparing smears from the active lesion or a touch preparation of a biopsy from the edge of the ulcer, allowing the preparation to air dry, then fixing in methanol and staining with Giemsa stain, or by culture.

Clinical Course and Treatment

The lesions of granuloma inguinale grow more rapidly during pregnancy (O'Farrell and Moi 2016) and in patients with concurrent HIV (Basta-Juzbasic and Ceovic 2014), in whom the lesions may persist longer and require a longer duration of treatment. In rare cases, the organisms may disseminate to involve other organs, most commonly liver and bone (O'Farrell and Moi 2016). Treatment with

appropriate antibiotics, continued until the lesion is completely healed, is curative.

Lymphogranuloma Venereum (LGV)

LGV is a sexually transmitted disease endemic to Africa, Asia, and Central and South America, caused by Chlamydia trachomatis types L1, L2, and L3. It is uncommon in the West, but sporadic outbreaks have been noted in recent years, principally involving HIV-positive homosexual male patients (French et al. 2005).

Clinical Features

The disease classically manifests in three phases, following an incubation period of 3–30 days. The initial lesion is a painless papule which may progress to an ulcer and heals within a week. Two to 6 weeks later, a second phase may develop, usually characterized by painful inflammation of inguinal lymph nodes which may progress to the development of draining sinus tracts. This classic presentation with inguinal involvement has become increasingly uncommon, however, especially in women (Basta-Juzbasic and Ceovic 2014), with proctitis, vaginitis, and cervicitis accompanied by constitutional symptoms now more frequently observed. A third phase of the disease may develop in patients who continue untreated, consisting of progressively worsening proctocolitis and abscess development with lymphatic obstruction and fibrosis and stricture of the vagina and rectum.

Microscopic Findings

The initial lesion of LGV heals rapidly and is very rarely biopsied. Even if it is, the histology is nonspecific, showing giant cells along with lymphocytes and plasma cells in the inflammatory infiltrate surrounding the ulcer (Fig. 8). Older lesions may exhibit extensive fibrosis of the dermis and sinus tracts. Although the organisms are extremely difficult to identify on light microscopy, evaluation with special stains or other techniques is important to rule out other infectious disease with a similar presentation. The diagnosis rests on the results of serologic testing as well as identification of the organism in culture or by PCR testing.

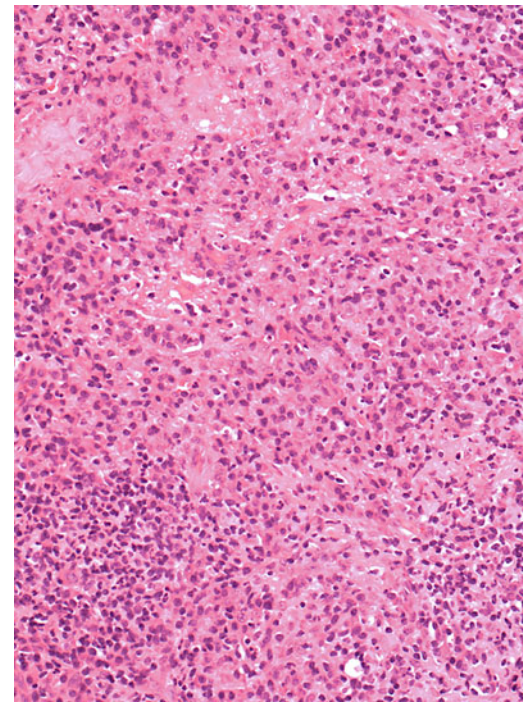


Fig. 8 LGV An intense superficial and deep chronic inflammatory infiltrate composed predominantly of lymphocytes and plasma cells is present

Clinical Behavior and Treatment

Treatment is with antibiotics and may also include aspiration or incision and drainage of buboes to prevent progression to deep ulcers and fistulas and aid in healing. Timely treatment will prevent progression to the third, potentially disfiguring, phase of disease.

Chancroid

Endemic in Africa, Asia, and the Caribbean, where it may be responsible for up to 56% of genital ulcer disease (Mohammed and Olumide 2008), chancroid, a sexually transmitted disease caused by *Haemophilus ducreyi*, is relatively rare in the West.

Clinical Features

The disease presents after a 3- to 7-day incubation period, initially as a small papule which progresses to a pustule and then to a soft painful ulcer. Lesions may be single or multiple and tend to be small, measuring approximately

1–2 mm in diameter, but multiple lesions may coalesce to form ulcers approaching 3 cm in diameter. In women, the ulcers may involve the fourchette, labia, vestibule, clitoris, and perianal area and are often subclinical. In 40–50% of patients, painful inguinal adenopathy develops a few days to 2 weeks following the ulcer (Mohammed and Olumide 2008; Basta-Juzbasic and Ceovic 2014).

Microscopic Findings

Histologic examination of the skin lesions shows a three-layered structure to the ulcer. Superficially, there is an ulcer bed containing abundant neutrophils, beneath which is a layer of granulation tissue. In the deepest part of the lesion is a chronic inflammatory infiltrate consisting primarily of lymphocytes and plasma cells. Gram or Giemsa stains may reveal the gram-negative organisms, which may be present in large numbers in pairs and in parallel chains in the more superficial portion of the lesion, but culture and PCR are more sensitive and specific methods of diagnosis.

Clinical Course and Treatment

Treatment with antibiotics is curative in immunocompetent individuals. The disease is currently much more frequently encountered in HIV-positive patients, however, in whom the lesions are more numerous, heal poorly, and may fail to respond adequately to treatment (Mohammed and Olumide 2008).

Tuberculosis

Tuberculosis of the female genital tract is a common cause of pelvic inflammatory disease and infertility in some parts of the world but is very uncommon in most developed countries. It most commonly affects the fallopian tubes and endometrium (Manoj et al. 2008); vulvar involvement is exceedingly rare, present in less than 2% of tuberculosis cases with pelvic involvement (Shen et al. 2011; Manoj et al. 2008). It is usually the result of hematogenous spread from a primary pulmonary infection with *Mycobacterium tuberculosis*, which has often healed by the time the pelvic disease is detected, but autoinoculation is thought to be responsible in some cases. Immunosuppression may play a role in susceptibility, as a case of vulvar tuberculosis has been described in a renal transplant patient (Wilkinson and Stone 2008), and hormones may influence development as well, as most cases present in the reproductive age range (Manoj et al. 2008)

Clinical Features

Vulvar tuberculosis may present as ulcerative lesions or swellings with multiple draining sinuses or as bulky exophytic lesions with associated lymphatic obstruction.

Microscopic Findings

Diagnosis usually can be made by biopsy of the involved tissues, which will reveal the characteristic caseating granulomas with Langhans giant cells. The mycobacteria can be identified on acid-fast stain, but this is far less reliable than isolation of the organism in culture.

Clinical Course and Treatment

Resection of lesions with a 6-month course of antitubercular drugs is curative (Manoj et al. 2008).

Miscellaneous Bacterial Infections

Erythrasma is a superficial skin infection caused by *Corynebacterium minutissimum*, which presents as an asymptomatic macular pink-brown rash. Because it has a predilection for the skin folds, the vulvar area may be involved, but the diagnosis is generally made on clinical grounds and biopsy is rarely necessary.

Erysipelas is a manifestation of infection of the skin with hemolytic streptocci or *Staphylococcus aureus*. It presents as a sharply marginated area of erythema, often associated with fever, malaise, chills, and nausea. The infection may progress to involve the subcutis, resulting in cellulitis, in which case the erythema is less well-defined and the involved area becomes edematous and painful.

Skin infection with hemolytic streptococci or *Staphylococcus aureus* can also result in impetigo. On the vulva, impetigo is usually restricted to the hair-bearing skin, where it appears as small vesiculopustules which quickly rupture and develop a golden brown crust.

Rare cases of botryomycosis, an ulcerative infection of the skin caused by *S. aureus, P. aeruginosa, E. coli, Streptococci*, or *Proteus* species, have been reported to involve the vulva (Elas et al. 2014). This disease is best recognized by examination of the purulent drainage from the ulcer, in which the characteristic "granules" of bacteria may be identified.

Necrotizing fasciitis may occur in the vulva and perineum in the skin damaged by recent surgical intervention or trauma. Most vulvar cases are caused by polymicrobial infection, including anaerobic species (Nakayama and Busse 2010). Predisposing factors include diabetes mellitus, immunosuppression, peripheral vascular disease, increased age, hypertension, obesity, and radiation exposure. Initially, necrotizing fasciitis may appear as mild cellulitis or edema with inflammation, frequently associated with severe pain out of proportion to the degree of apparent tissue damage. Fever may or may not be present. The disease typically progresses rapidly despite treatment with antibiotics and must be recognized quickly, as a delay in diagnosis without therapy carries a nearly 50% mortality rate (Stephenson et al. 1992). Prompt, aggressive surgical debridement radical excision of the infected tissue and broad-spectrum systemic antibiotic therapy offers the only chance of cure, but even with appropriate treatment, mortality rates are reported to range from 20 to 40% (Sultan et al. 2012).

Viral

Condyloma Acuminatum

Condyloma acuminatum is an exophytic lesion of the skin, or, less commonly, the mucous membranes, caused by infection with low-risk subtypes of HPV, most commonly types 6 and 11. The frequency of vulvar condyloma acuminatum varies according to the population but is generally over 1%.

Many risk factors for the development of vulvar condyloma have been identified. As a sexually transmitted disease, the risk of condyloma acuminatum is increased with increasing numbers of sexual partners. The risk is also increased in patients with HPV-related lesions elsewhere in the lower anogenital tract; up to 50% of women with vulvar condyloma acuminatum also have past, concurrent, or subsequent diagnoses of cervical or vaginal squamous intraepithelial lesions (Mittal et al. 2013). Other commonly associated conditions are vaginitis, pregnancy, diabetes, oral contraceptive use, and poor hygiene. Immunosuppression is an increasingly common predisposing condition, and women with HIV, organ transplants, or autoimmune diseases (Santana et al. 2011; Lyrio et al. 2013) often struggle with widespread lesions throughout the lower anogenital tract that can be very difficult to eradicate.

When condyloma acuminatum is detected in a child, sexual abuse must be considered, but other modes of transmission have also been demonstrated. Vertical transmission of the virus, either in utero or intrapartum, is possible (Jayasinghe and Garland 2006), and when it occurs, the virus may remain dormant for years before visible lesion develops (Hornor 2004). Many pediatric cases have been shown to contain types 1 and 2, subtypes more common in common skin warts, and frequently the patient or caregiver is found to have common warts (Allen and Siegfried 1998; Stefanaki et al. 2012), suggesting transmission by autoinnoculation and or nonsexual contact. There is some evidence that the disease may also be transmissible by fomites (Jayasinghe and Garland 2006).

Early data on the effects of HPV vaccination strongly suggests that condylomata acuminata may become increasingly less common. In Denmark and Australia, where robust vaccination programs have reached 70–85% of the target population, marked reductions in the diagnosis have already been reported (Ali et al. 2013; Baandrup et al. 2013; Read et al. 2011), and recent data suggests rates are dropping in the USA as well (Flagg et al. 2013).

Clinical Features

The lesions are usually asymptomatic and frequently multiple and multifocal. They often come to clinical attention because of considerable enlargement during pregnancy (Garland et al. 2009; Hoy et al. 2009). Any area of the vulva, as well as the vagina, cervix, urethra, and anal canal, may be affected. The lesions may be red, white, gray, or brown and vary in size from millimeters to several centimeters (Fig. 9). Application of a dilute

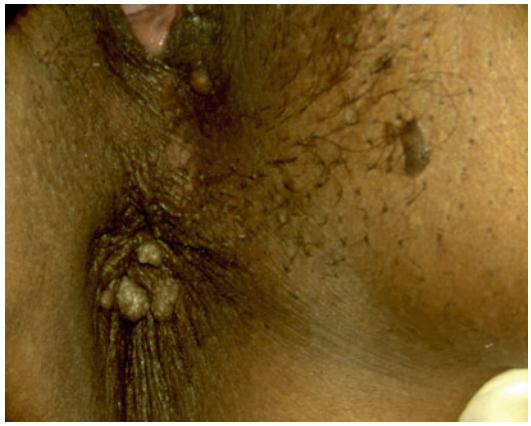


Fig. 9 Perianal condylomata. The exophytic lesions have a corrugated, irregular surface. (Photograph courtesy of Dr. Jaqueline Castagno, University of Florida)

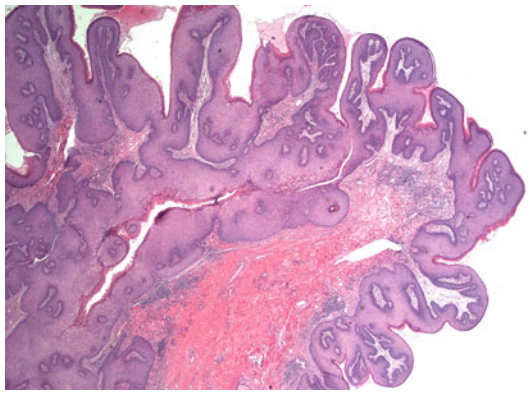


Fig. 10 Condyloma acuminatum. This low-power magnification shows the complex papillary architecture, with central fibrovascular stalks lined by thickened epithelium

solution of acetic acid will impart a white appearance to the abnormal epithelium, which may aid in identification. On occasion, multiple lesions may coalesce into large plaques, an occurrence more common in diabetic or immunosuppressed patients.

Microscopic Findings

On histologic examination, the lesion consists of complex branching fibrovascular cores covered with acanthotic squamous epithelium, frequently with accompanying hyperkeratosis and parakeratosis (Fig. 10). The pathognomonic feature is koilocytic atypia, characterized by enlarged, hyperchromatic nuclei with irregular, wrinkled nuclear membranes accompanied by a region of perinuclear clearing or "halo," usually located in the upper third of the epithelium (Fig. 11). These cellular changes are the morphologic manifestation of HPV production in the infected cells but may be minimal to absent in some cases (Medeiros et al. 2005). Basal and parabasal hyperplasia, with increased mitotic figures confined to the lower third of the epithelium, and cytoplasmic maturation beginning to appear in the middle third and relatively normal maturation of the upper third are characteristic, and prominent intracellular bridges may be noted. Dyskeratotic cells may be seen, and a subepithelial chronic inflammatory infiltrate is commonly identified.

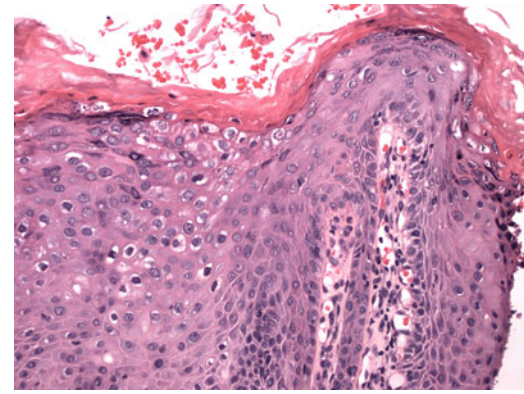


Fig. 11 Condyloma acuminatum. At higher power magnification, the characteristic koilocytic change, with perinuclear clearing surrounding enlarged, irregularly shaped hyperchromatic nuclei, is seen in the superficial layers of the epithelium

Differential Diagnosis

Other benign exophytic lesions of the vulva, such as fibroepithelial polyp, vestibular papilloma, and seborrheic keratosis, will lack the basal hyperplasia and koilocytic atypia typical of condyloma. In cases where the morphology is not sufficiently distinctive, immunohistochemical staining for Ki-67 may also be of further assistance in differentiating these lesions from condyloma. Because HPV infection activates the cell cycle in order to accomplish viral reproduction, a process which occurs in the maturing squamous cells, Ki-67 will be reactive in some cells in the upper levels of the epithelium in condylomata/low-grade squamous intraepithelial lesions (LSIL) while in normally epithelium and other benign squamous lesions, expression of Ki-67 is limited to the basal and parabasal cells.

Although high-grade squamous intraepithelial lesions (HSIL) and squamous cell carcinomas with warty morphology may show marked koilocytic atypia in the superficial cells, they are distinguished from condylomata by greater immaturity of the epithelium, the presence of abundant, frequently atypical, mitotic figures, particularly if present in the upper layers of the epithelium, and, in the case of carcinoma, the presence of invasion into the underlying tissue.

It should be remembered that, although uncommon, lesions with the typical morphologic features of condyloma can contain areas of associated HSIL. Such lesions are almost exclusively seen in immunosuppressed patients (Maniar et al. 2013), and for this reason, it is advised that even lesions which appear to be benign condylomata in such patients ought to be biopsied to ensure the absence of a high-grade component. Even when these lesions are biopsied, the extensive condylomatous component may be so distant from other abnormal areas that the high-grade component may be missed on sampling. The same may occur on a microscopic level when a small focus of adjacent high-grade lesion is missed when the slides are examined due to the relative abundance of condylomatous lesion. It is speculated that lesions like these may be responsible for previously reported cases of condyloma containing high-risk HPV.

Clinical Course and Treatment:

Condylomata acuminata may regress spontaneously but usually persist and may increase in size or number over time. They are not considered premalignant and do not progress to HSILs or carcinoma. Topical application of dilute podophyllin, imiquimod, concentrated halogenated acetic acid (trichloroacetic acid), or sinecatechins (Lacey et al. 2013) can be used for the treatment of small vulvar condylomata. Response to therapy may be decreased in immunosuppressed patients and patients with concurrent cervical HPV infection (Koo et al. 2016). Larger lesions and those refractory to topical treatments may be removed or eradicated by electrosurgery, cryosurgery, laser ablation, or surgical excision (Lacey et al. 2013). The overall recurrence rate is reported as 20–30% (Lacey et al. 2013), with higher rates reported in patients with a higher viral load (Koo et al. 2016) and lower rates in patients treated with surgical excision.

Herpesvirus

Genital infection with HSV was once almost exclusively caused by HSV type 2, and HSV type 1 was limited to oral lesions. Today, probably due to changing patterns of sexual behavior, genital infection with HSV type 1 is increasingly common, especially in younger cohorts, comprising approximately half of new cases in some developed countries (Gupta et al. 2007), although vulvar infection with HSV type 2 is still approximately six times more common than with HSV type 1. Primary genital infection with HSV type 1 is more frequent in women, and more often symptomatic (Fatahzadeh and Schwartz 2007), but also less likely to recur. Antibodies to one type of HSV provide some protection against the other, leading to a decreased frequency of infection with a second type, and may result in decreased severity and duration of the newly acquired infection (Fatahzadeh and Schwartz 2007). Although approximately 20% of the US population has been infected by HSV 2 by age 40, and up to 85% have been infected by HSV 1 by age 60, the frequency of vulvar involvement is unknown, and the majority of infections appear to be subclinical (Fatahzadeh and Schwartz 2007; Maccato and Kauffman 1992; Nettina 1998).

Clinical Features

The disease typically presents 4–7 days after exposure, with a prodrome of constitutional symptoms including fever, headache, muscle aches, and a painful, erythematous swelling of the vulva, followed by the eruption of clusters of papules and vesicles which evolve into exquisitely painful ulcers (Fig. 12). Lesions may involve the anus, urethra, bladder, cervix, and vagina, as well as the vulva, and may be accompanied by dysuria and vaginal discharge.

Concurrent HIV infection may drastically alter the presentation of HSV-related disease. HIV-positive patients tend to have more severe and more frequent outbreaks, and to develop more extensive lesions which may take longer to resolve (Domfeh et al. 2012; Fatahzadeh and Schwartz 2007). They may also

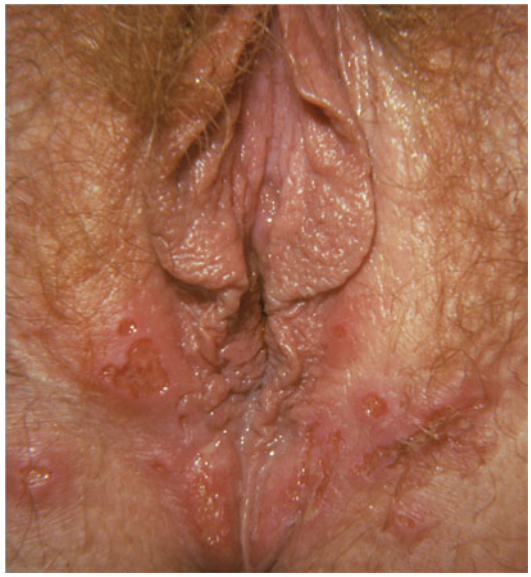


Fig. 12 Herpes simplex infection of the vulva. Numerous small, shallow ulcers on an erythematous base are visible on the inferior labia majora, labia minora, and perineum

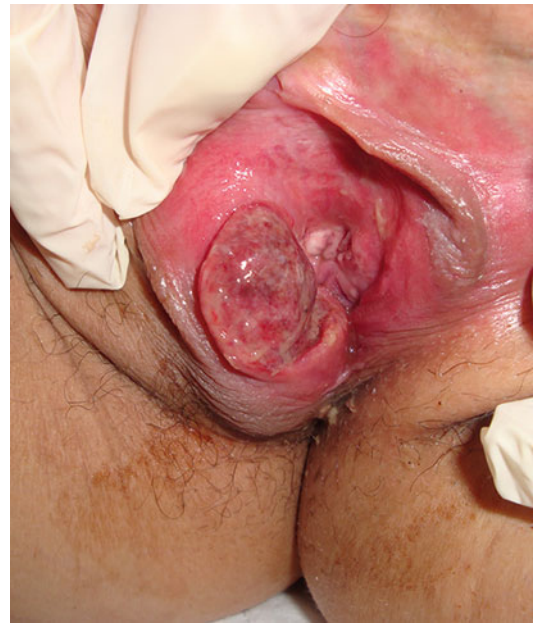


Fig. 13 Hypertrophic chronic vegetative lesion (HCVL) and atypical manifestation of herpes infection. The lesion is present on the medial surface of the labium minus and shows minute surface ulcerations. (Reprinted with permission from Selim et al. 2015)

develop lesions with atypical symptomatology or morphology, including painless lesions, fissures, patchy erythema, furuncles (boils), wart-like lesions, or diffusely and deeply ulcerating lesions (Domfeh et al. 2012; Fatahzadeh and Schwartz 2007). Of most concern to the pathologist may be the hypertrophic, mass-forming lesions sometimes referred to as hypertrophic chronic vegetative lesion (HCVL). Clinically, these lesions present as exophytic masses, measuring several centimeters in greatest dimension (Fig. 13), which may mimic warts or squamous cell carcinoma clinically (Domfeh et al. 2012; Mosunjac et al. 2009; Gomes do Amaral et al. 2009; Strehl et al. 2012; Tangjitgamol et al. 2013).

Microscopic Findings

A sample from the margin of the ulcer is most likely to reveal the pathognomonic findings. Infected cells show homogenization of the nuclear chromatin resulting in a "ground glass" appearance, which then progresses to the more typical eosinophilic intranuclear inclusion body. Multinucleation is also a characteristic feature (Fig. 14). Cytologic evaluation of the scraping of the base and edges (Tzank preparation) of a fresh ulcer, or freshly opened vesicle, may also show the characteristic cellular changes. Over time, the infected cells undergo karyorrhexis and lysis, and samples taken in the late ulcerative phase may not, therefore, always show the intranuclear inclusions.

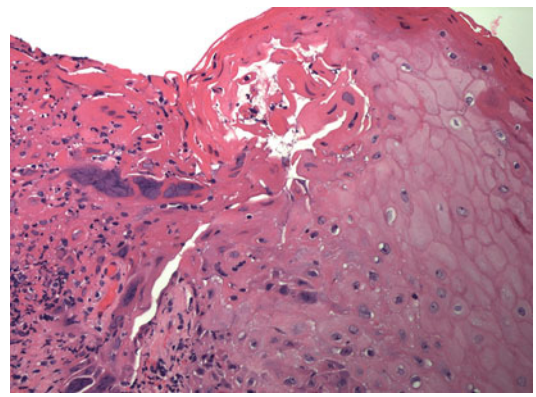


Fig. 14 The cellular changes of herpes simplex infection. Several multinucleated forms showing the characteristic homogenized glassy cytoplasm are present at the edge of this herpetic ulcer

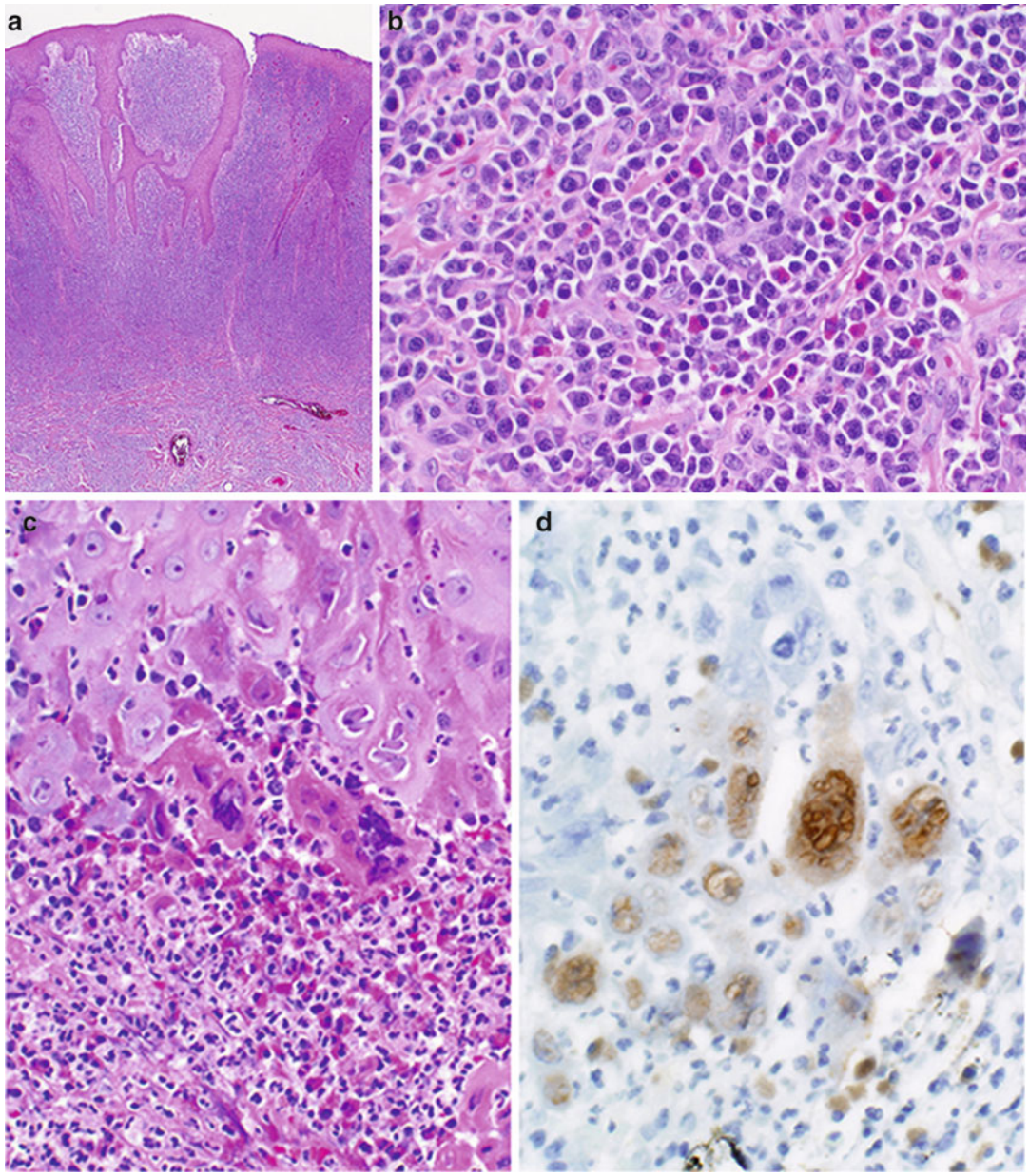


Fig. 15 Microscopic features of the hypertrophic chronic vegetative herpes lesion illustrated in Fig. 13. There is pseudoepitheliomatous hyperplasia **(a)** overlying a dense lymphoplasmacytic infiltrate **(b)**. The cytopathologic changes of HSV are seen focally **(c)**, and immunohistochemical stain for HSV confirms the diagnosis **(d)**. (Reprinted with permission from Selim et al. 2015)

The histologic features of the atypical lesions seen in HIV-positive patients are significantly different than those of the typical lesion. The large exophytic HCVL show a markedly thickened, hyperkeratotic epithelium, overlying a fibrotic, thickened dermis, with a dense inflammatory infiltrate of plasma cells and lymphocytes. Only small areas of ulceration, in which the characteristic viral changes may be identified, are present in such lesions (Fig. 15).

Morphologic changes seen with HSV infection are not reliable in separating primary from secondary infection or in distinguishing HSV type 1 from type 2 infection, nor can they differentiate the lesions of herpes zoster, which may involve the vulva as well, though only rarely, but immunohistochemical stains can be used to distinguish the type of virus present in tissue, cytologic preparations, or cultures when necessary. Viral culture has a relatively low sensitivity, however, and only about 80% of primary infections and 25–50% of recurrent infections can be identified this way (Gupta et al. 2007). PCR is the preferred method to identify the virus, as it is more sensitive and faster than culture (Fatahzadeh and Schwartz 2007; Gupta et al. 2007; Hope-Rapp et al. 2010).

Clinical Course and Treatment

Untreated, the ulcers of the initial episode heal in approximately 2–6 weeks, after which the virus lies dormant in regional sensory and autonomic ganglia. A 7–10-day course of systemic treatment with the antiviral agents acyclovir, valacyclovir, or famcyclovir can speed healing, decrease viral shedding, and decrease the incidence of new lesions, but these drugs do not prevent or eradicate latent infection, and they are not curative. Periodic reactivation of the virus is likely, leading to subsequent recurrences, the rate of which decreases with time since the primary infection (Gupta et al. 2007). Atypical lesions associated with concurrent HIV infection may not respond to conventional treatment; these patients may require higher doses of antiviral agents and longer durations of treatment, and some may require the use of alternative antiviral agents. Surgery may also be considered for large atypical lesions refractory to therapy.

Molluscum Contagiosum

Clinical Features

Molluscum contagiosum is a viral infection of the skin which manifests after an incubation period of 14–50 days as small, smooth papules (3–6 mm in diameter) with a central punctum or umbilication. They generally are multiple and separate, although they may be single. Rare plaque formations, made up of 50–100 individual clustered lesions, also have been described. In children, the lesions may develop anywhere in the skin, and the route of transmission is from close contact. Genital involvement is unusual in children (Zhuang et al. 2015). In adults, however, the genitals are usually the only site involved and the disease is almost exclusively transmitted by sexual contact (Bast-Juzbasic and Ceovic 2014). On the vulva, the keratinized surfaces of the labia majora, labia minora, and mons are most frequently affected. Lesions are usually asymptomatic, but may be pruritic, and excoriation from excessive scratching may facilitate secondary bacterial infection, which may mask the underlying condition and confound the diagnosis.

Microscopic Findings

Clinical diagnosis usually does not require biopsy, but when biopsy is performed, the histomorphology is distinctive (Fig. 16). The central dimple of the lesion can be seen histologically if the lesion is carefully bisected. Within the dermis, there often is a marked vascular response with endothelial proliferation and perivascular inflammation. In recent infections, the lesions demonstrate marked acanthosis and the characteristic eosinophilic intracytoplasmic viral inclusions (Henderson–Patterson bodies), which may also be identified in scrapings from the interior of the lesions.

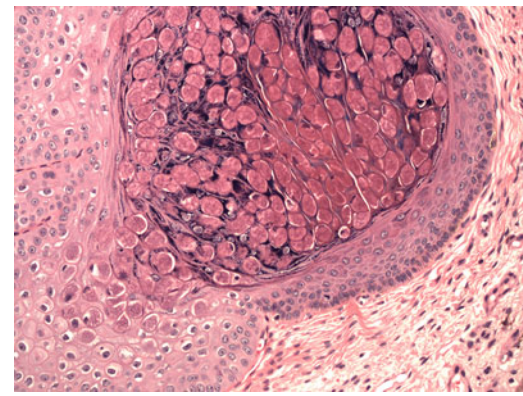


Fig. 16 Molluscum contagiosum. The center of the lesion shows the characteristic eosinophilic viral inclusions (Henderson–Patterson bodies)

Clinical Course and Treatment

The lesions are infectious as long as they are present, and although most lesions of molluscum contagiosum regress spontaneously within months to years, many patients are anxious to be rid of them sooner. Numerous treatment options are available to speed resolution, including curettage, cryosurgery, and topical agents. Responses are variable, and more than one treatment modality may be needed to successfully eradicate the disease.

Varicella (Herpes Zoster)

Vulvar shingles, caused by the involvement of the vulva by varicella, the etiologic agent of chicken pox, is rare. The lesions represent reactivation of virus which has been dormant in the sacral ganglia. The prodromal vulvar pain, without apparent physical findings, may at first simulate vestibulitis, but the subsequent eruption of vesicles and ulcers soon distinguishes it. Patients are usually postmenopausal and/or immunosuppressed and the vesicles are characteristically unilateral. The histologic and cytologic findings are indistinguishable from HSV, but immunohistochemistry with virus-specific antibody or PCR can differentiate them when necessary.

Cytomegalovirus

Cytomegalovirus (CMV) is a rare cause of ulcerative cervicitis and vulvovaginitis which may mimic HSV infection clinically (Abou and Dallenbach 2013). The histopathologic findings are similar, except that the cytologic changes caused by CMV are both intranuclear and cytoplasmic, multinucleated forms do not occur, and the viral inclusions also may be seen involving vascular endothelial cells, as well as the epithelial cells. The diagnosis can be confirmed in tissue by immunohistochemical staining using specific antibodies to CMV, PCR of swabs collected from active lesions, or by isolation in culture.

Epstein–Barr Virus

Primary infection with Epstein–Barr virus (EBV) is occasionally the cause of ulcerations of the labia minora which may or may not be accompanied by the systemic symptoms characteristic of infectious mononucleosis. The ulcers are usually more than a centimeter in diameter (Halvorsen et al. 2006), necrotic, deep, and painful. The median age of affected patients is 14.5 years old, and in most patients there is no history of recent sexual activity (Halvorsen et al. 2006). Involvement of the vulva is presumed to occur via hematogenous spread, but sexual transmission cannot be completely ruled out in all cases.

The ulcers appear very early in the disease, usually before serology can detect the infection, and heal spontaneously in 3–4 weeks (Halvorsen et al. 2006; Sand and Thomsen 2017; Taylor et al. 1998). Viral culture or PCR may identify the virus (Halvorsen et al. 2006; Sand and Thomsen 2017). Histological findings are nonspecific, and the lesion is extremely unlikely to be encountered as a biopsy specimen.

Fungal

Fungal infection of the vulva may cause chronic inflammatory conditions of the vulvar and perianal skin. The most common agents are *Candida* species. Recurrent or chronic vulvar candidiasis may cause the involved mucosa to become atrophic and painful, with a glazed red appearance. Painful fissuring in the periclitoral area, interlabial sulcus, and around the introitus may develop and may be a clue to the diagnosis (Margesson, 2006). Dermatophytes are less common, and often of zoonotic origin, with *Microsporum canis* and *Trichophyton mentagrophytes* the most commonly encountered (Sand and Thomsen 2017). Dermatophytosis usually involves the hair-bearing skin, producing follicular papulopustular lesions which may coalesce into elevated erythematous scaly plaques. Pityriasis versicolor (tinea versicolor), caused by *Malassezia* species, has also been reported on the vulva (Day and Scurry 2014). Fungal infections of the vulva rarely require biopsy, and accurate diagnosis generally can be accomplished by microscopic examination of skin scrapings placed in 10% potassium hydroxide or by appropriate culture methods. When biopsy is performed, the presence of neutrophils in the epidermis may suggest a fungal

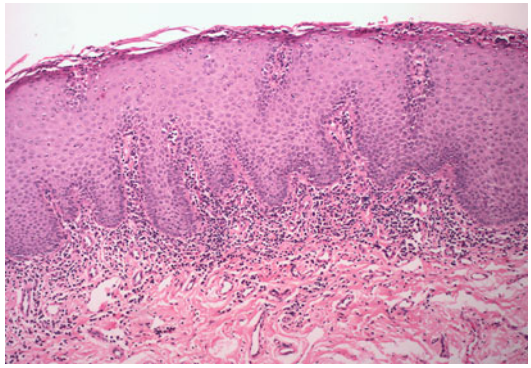


Fig. 17 Fungal infection of the vulvar skin. Numerous intraepithelial neutrophils are present, which can be a useful clue to a fungal etiology. The differential diagnosis includes psoriasis, which can look very similar (see Fig. 18a, b), and definitive diagnosis requires identification of the fungal organisms on special stains

etiology (Fig. 17), and performance of silver or periodic acid–Schiff (PAS) stain may reveal the organisms. Topical antifungal creams are the usual therapy.

Parasitic

Pediculosis pubis, or pubic lice, caused by infestation of *Pthirus pubis*, is not uncommon, but rarely generates a specimen for histologic examination, as the nits, nymphs, and adult lice may be visualized with the naked eye or with the assistance of a magnifying glass.

Other parasitic infections of the vulva are quite rare. Children infected with *Enterobius vermicularis* (pinworm) frequently experience severe vulvovaginal pruritus, which may awaken them at night, thought to be related to migrating worms. Examination of the vulvar vestibule and vagina in such cases reveals marked inflammation, but only rarely is the parasite identified in the vulvar tissue. A granuloma secondary to *Enterobius* eggs has been reported involving the vulva (Sun et al. 1991). Skin lesions on the vulva from penetration of the infective cercariae of schistosomiasis, usually *Schistosoma mansoni*, may be encountered in endemic areas, in which the parasite may be found within the epidermis on biopsied samples. Cutaneous myiasis of the vulva, secondary to infestation of the larval form of the muscoid fly and Sarcophaga, has also been reported and can be diagnosed by recognition of the larva extracted from the vulvar tissues (Cilla et al. 1992; Koranantakul et al. 1991).

Inflammatory Dermatoses

The inflammatory dermatoses are among the most common dermatologic disorders, and vulvar involvement is frequent. The recognition of these disorders, both clinically and histologically, is significantly more difficult on the vulvar skin than in extragenital sites, due in large part to the particular local conditions. The vulvar skin is confined in an occlusive environment, in which it is subject to high levels of moisture, friction, and other irritations, which frequently combine to induce an aberrant appearance of inflammatory dermatoses in this region. Features which are characteristic on nongenital skin may be obscured or even absent. At the same time, reactive changes and superinfection are much more likely to be superimposed on vulvar lesions, creating a complex tangle of symptoms and findings which can be difficult to tease apart. Biopsies of inflammatory dermatoses of the vulva, consequently, are frequently inconclusive, and arriving at a specific diagnosis often requires careful clinicopathologic correlation as well as observation over time. The job of the pathologist in these cases is not so much to establish an unequivocal diagnosis as to narrow the differential.

Recognition of specific histologic patterns has long been used by dermatopathologists as the first step in classification of dermatologic conditions, leading the International Society for the Study of Vulvovaginal Diseases (ISSVD) to establish its first classification scheme based for vulvar dermatoses based on histologic pattern (Lynch et al. 2006). The original 2006 ISSVD classification of the inflammatory dermatoses is simplified to include only those disorders most likely to be encountered on vulvar biopsies, and is the basis for Table 2, which also includes some less common disorders worthy of consideration. Following this framework, the disorders are presented below in groups classified by the dominant histologic pattern.

Table 2 A summary of vulvar dermatoses classified by histologic pattern. The conditions on the left are those included in the 2006 ISSVD classification. On the right are additional conditions presented in this chapter

2006 ISSVD classification of vulvar dermatoses[a]	Less common entities (not included in the 2006 ISSVD classification)
Spongiotic pattern	
Atopic dermatitis **Allergic/irritant contact dermatitis**	
Acanthotic pattern	
Psoriasis **LSC (primary or secondary)**	
Lichenoid pattern	
LS **LP**	Fixed drug eruption
Dermal homogenization/sclerosis pattern	
LS	Morphea
Vesiculobullous pattern	
Pemphigoid, cicatricial type (mucous membrane pemphigoid) **Linear IgA disease**	Bullous pemphigoid Pemphigoid gestationis Pemphigus Bullous systemic lupus erythematosus (SLE)
Acanthotic pattern	
Hailey–Hailey disease **Darier's disease** **Papular genitocrural acantholysis (papular acantholytic dyskeratosis)**	
Granulomatous pattern	
Crohn's disease **Melkersson–Rosenthal disease (granulomatous vulvitis)**	Sarcoid
Vasculopathic pattern	
Aphthous ulcers **Behçet disease** **Plasma cell vulvitis**	

[a]Adapted from Lynch et al. 2006

Spongiotic Pattern

Epithelial spongiosis is the result of intraepithelial edema. Clinically, spongiotic lesions present as eczematous dermatitides, with a wet, oozing surface. On the vulva, because it is usually closely covered, trapping of the moisture may result in maceration of the surface, which may disguise the underlying condition. Microscopically, spongiosis is evidenced by increased space between epithelial cells, representing the area of fluid accumulation.

Table 3 Common vulvar allergens and irritants. Many substances can act as either an allergen or an irritant, depending on the sensitivity of the patient

Common vulvar allergens and irritants
Fragrances
Topical anesthetics
Preservatives
Topical antifungals and other antibiotics
Emollients
Metals (nickel, gold)
Body fluids
Soaps and detergents
Lubricants
Excessive heat

Allergic/Irritant Contact Dermatitis

Clinical Features

Contact dermatitis is the most commonly encountered spongiotic dermatitis of the vulva, affecting approximately 15–54% of women (Ball et al. 2015; Connor and Eppsteiner 2014). Vulvar contact dermatitis may be of an allergic type (allergic contact dermatitis, ACD) or an irritant type (irritant contact dermatitis, ICD), with the latter being the more common of the two. The allergic type is a cell-mediated response to sensitizing agents, which can include a number of soaps, topical medications and remedies, or components thereof (Moyal-Barracco and Wendling 2014; O'Gorman and Torgerson 2013; Foote et al. 2013; Bauer et al. 2005). The irritant type is due not only to the presence of an irritant, but also to underlying skin damage and subsequent loss of barrier function, as may be seen in urinary incontinence, and occasionally in association with sanitary napkin use during menstruation (Wakashin 2007). A list of selected common potential allergens and irritants is presented in Table 3.

The presentation of ICD and ACD is variable, depending on the severity and duration of the process. Acute ICD develops within minutes to hours of the exposure, while those of ACD take 24–48 h to develop. The lesions of ICD tend to be well-circumscribed, confined to the area of contact, more likely to be painful, and less likely to develop vesicles and bullae, while those of ACD are more poorly demarcated, more likely to be pruritic, and more likely to develop vesicles and bullae. Superficial erosion or ulceration may be present in both.

Not infrequently, the clinical appearance is normal or only minimally altered (Ball et al. 2015), despite significant symptomatology.

Microscopic Findings

The pathologic findings are also variable and depend on the age of the lesion. Spongiosis may be minimal at first, progressing to pronounced dermal edema with the formation of microvesicles, and regressing again with more time. In long-standing contact dermatitis, LSC (see section "Lichen Simplex Chronicus") often supervenes, with prominent acanthosis and hyperkeratosis.

Clinical Course and Treatment

The symptoms of ICD and ACD will continue until contact with the offending agent can be eliminated, a process which may take some time to achieve. All possible exposures must be eliminated by the patient, which can necessitate quite extensive changes and can be quite disruptive, demanding the elimination of every soap, shampoo, laundry product, lotion, lubricant, topical ointments and creams, and even many items of clothing, among other things, until each can be exonerated by the result of patch testing or by slow reintroduction one at a time. A variety of therapies may be used for symptomatic control until the allergen or irritant can be identified. Vaseline or zinc oxide may be used to form a barrier to potential exposures, oral over-the-counter antihistamines may be used to control itching, and nonsteroidal anti-inflammatory agents may be used to control pain. Sitz baths and cold compresses may also provide relief. Unresponsive pain may be treated with tricyclic antidepressants and anticonvulsants. Finally, topical corticosteroids, or in severe cases localized injection or systemic steroid administration, are also usually part of the management, keeping in mind that in rare cases topical corticosteroids may themselves be the cause of the allergen or irritation.

Atopic Dermatitis

Clinical Features

With 85% of patients presenting before age 5, and the majority of cases remitting by adolescence, atopic dermatitis is predominantly a disease of childhood. The disease first manifests in adulthood in only 2–8% of patients (Arkwright et al. 2013). The disorder may involve the vulvar skin, but very few cases have been reported in the literature to date, and the frequency of vulvar involvement is unknown. The physical findings may be limited to dryness and scaling, but thickening of the skin with localized excoriation may be evident if the vulva has been irritated by scratching.

Microscopic Findings

Because the diagnosis is usually established by clinical findings and the appearance on the non-genital skin, vulvar biopsies are rarely performed on these patients. When they are, the pathologic findings are usually nonspecific. Spongiosis may be present. Within the dermis, lymphocytes and macrophages are present, and the density of the infiltrate tends to correlate with the severity and chronicity of the process. Eosinophils and mast cells also may be identified. Most often, superimposed lichen simplex chronicus (LSC) (see section "Lichen Simplex Chronicus") has developed in response to the chronic itching and scratching, masking the initiating condition.

Clinical Course and Treatment

Although 70% of children with atopic dermatitis show spontaneous remission before they reach adulthood, a minority of patients suffer lifelong disease with periodic exacerbations. There is no cure for the disease, but most patients' symptoms can be controlled using emollients and topical corticosteroids. In patients who do not show an adequate response, topical calcineurin inhibitors may be used in place of steroids. Rarely, severe, refractory disease requires systemic treatment with calcineurin inhibitors such as cyclosporine.

Differential Diagnosis of Spongiotic Dermatitis of the Vulva

Histology cannot always distinguish between ICD, ACD, and atopic dermatitis, but certain features favor a specific diagnosis. The presence of balloon cell change and dyskeratosis favors ICD, with the caveat that if such changes are severe fixed drug eruption (see section "Fixed Drug Eruption") and erythema multiforme (see section "Erythema Multiforme/Stevens–Johnson Syndrome") must

Table 4 Select features of use in the differential diagnosis of common spongiotic dermatoses of the vulva

Differential diagnosis of spongiotic dermatoses of the vulva						
Diagnosis	Pain	Pruritis	Demarcation of lesions	Presence of balloon cell change +/− dyskeratosis[a]	Formation of vesicles+/− bullae[b]	Concurrent involvement of nongenital skin
ACD	Rare	Common	Poor	No	Sometimes (containing eosinophils and Langhans cells)	No
ICD	Common	Rare	Sharp	Sometimes	No	No
Atopy	Rare	Invariably	Poor	No	No	Yes

[a]Rule out erythema multiforme
[b]Rule out vesiculobullous disease

be considered as well. Prominent vesicles containing eosinophils and aggregates of intraepidermal Langhan cells favor ACD (Moyal-Barracco and Wendling 2014; Hoang et al. 2014), although the former may also be seen early in the development of some vesiculobullous disorders, in which case immunofluorescent studies may be used to make the distinction. Spongiosis may be seen as a component of reactions to fungal infection, some drug reactions, arthropod bites, as well as in contact and atopic dermatitis. A careful search for fungal organisms, with the use of special stains such as PAS or silver stains if necessary, will easily establish the presence or absence of infection, and clinical history will help determine whether drug reactions or arthropod bites need to be considered. Spongiosis may also be seen in acantholytic disorders, but as acantholysis is not a feature of atopic or contact dermatitis, this finding will point to a different set of diseases altogether (see section "Acantholytic Pattern"). The differential diagnosis of spongiotic dermatoses is summarized in Table 4.

Acanthotic Pattern

Acanthosis refers to thickening of the epithelium, which presents clinically as thick white plaques. Histologically, two patterns of acanthosis may be recognized. In "regular acanthosis," sometimes also called "psoriasiform hyperplasia," the rete ridges are uniformly elongated, with all of them having the same length and width. In "irregular" acanthosis," the rete ridges are variable in length and width from one to the next. Whether regular or irregular, acanthosis takes time to develop and is therefore an indication of a chronic, rather than an acute, condition.

Psoriasis

Clinical Features

Psoriasis is a chronic immune-mediated disease which affects approximately 3.2% of the population of the USA (Young et al. 2017) and involves the genitalia in 30–40% of patients (Andreassi and Bilenchi 2014). The median age of onset in women is 25 years (Young et al. 2017), and the severity of disease often fluctuates with hormone levels, with exacerbations developing in puberty, postpartum, and menopause. Vulvar psoriasis may present in the classic form, most commonly on the mons, with sharply demarcated erythematous papules and plaques covered with silvery scale, which show punctate points of bleeding when the superficial scale is removed (Auspitz sign). More often, however, on other vulvar sites, is the inverse form, in which the scale is absent, and the lesions appear as flat red patches which may also be eroded or ulcerated. Symptoms of vulvar psoriasis may include itching, burning, and pain.

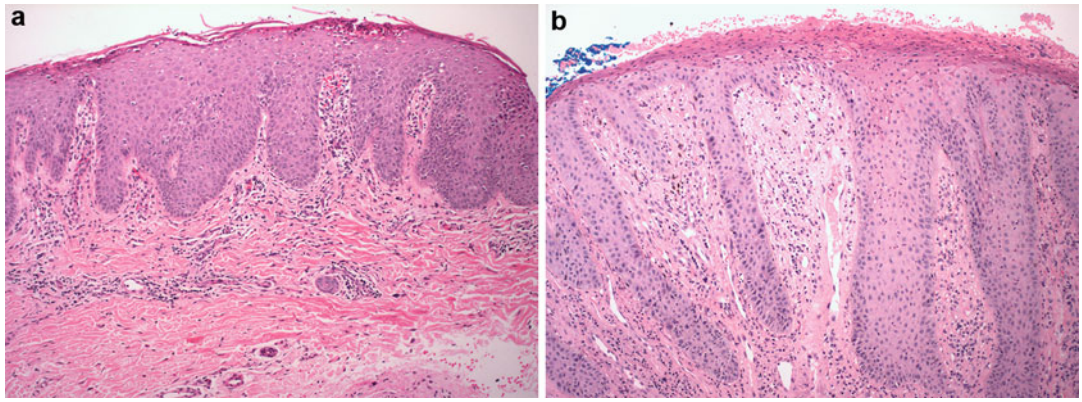


Fig. 18 **(a)** Classic psoriasis. The epidermis shows regular acanthosis, thinning of the suprapapillary plates, loss of the granular layer, and confluent surface parakeratosis with superficial collections of neutrophils (Munro microsabscesses). **(b)** Inverse psoriasis. This lesion shows the same features as classic psoriasis but with more even dispersion of neutrophils and a thicker parakeratotic surface

Microscopic Findings

In the classic form, well-developed lesions show the typical diagnostic features of confluent superficial parakeratosis with intraepidermal collections of neutrophils (Munro microabscesses), epidermal hyperplasia, loss of the granular layer, spongiotic pustules, and thinning of the suprapapillary plates (Fig. 18a). In the inverse form (Fig. 18b), diagnostic features may be less prominent or even lacking on biopsy (Andreassi and Bilenchi 2014; Moyal-Barracco and Wendling 2014).

Clinical Course and Treatment

A variety of treatments are available for psoriasis, but none is curative. Mild disease can be treated with a wide variety of topical agents, while more severe disease requires systemic immunosuppressive therapy with agents such as methotrexate or cyclosporine. Phototherapy is another effective adjunct or alternative to topical agents, but its use on the vulva, where the anatomy may make it difficult, is limited. Newer agents which target directly the cytokines responsible for the aberrant immune response are also available for use in moderate to severe disease, and have significantly improved outcomes.

Lichen Simplex Chronicus

Clinical Features

LSC is a reactive pattern induced by persistent rubbing or scratching in response to local itching. It may occur without a diagnosed cause of the initial itch (primary LS) or as the end point of many chronic pruritic conditions such as atopic or contact dermatitis, chronic fungal infections, LS, or LP. It most commonly involves the hair-bearing skin of the labia majora, mons pubis, and perianal region and may be confined to a focal area, appearing gray-white or reddened on clinical exam (Fig. 19). The skin markings are often accentuated, a sign of intradermal edema and chronic rubbing; excoriation and fissures are common.

Microscopic Findings

In addition to prominent acanthosis of the irregular type, the histopathologic features may include hyperkeratosis and hypergranulosis. Fibrosis of the papillary dermis, characterized by vertical orientation of the collagen fibers, is characteristic, and the capillaries in the papillary dermis also show a vertical orientation (Fig. 20). This orientation of the collagen fibers and capillaries of the papillary dermis is distinctive and a useful clue to the diagnosis (Ball et al. 2015). A chronic inflammatory infiltrate in the superficial dermis is usually present, but the

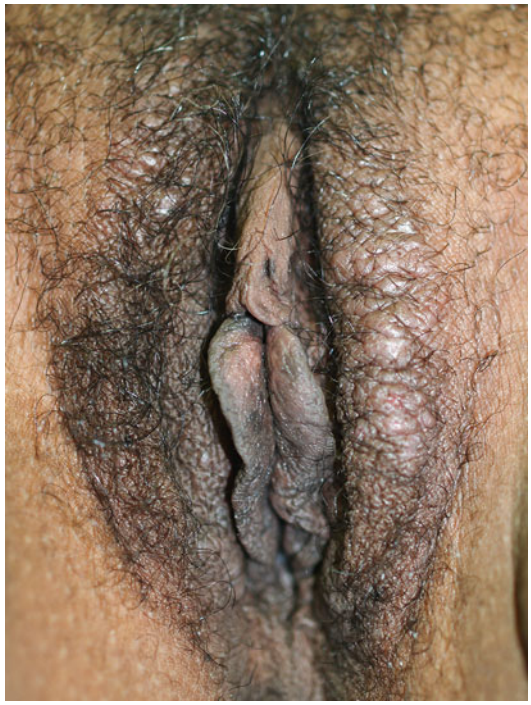


Fig. 19 The gross appearance of LSC. The left labium majus shows a thickened, grayish surface. (Reprinted with permission from Ball et al. 2015)

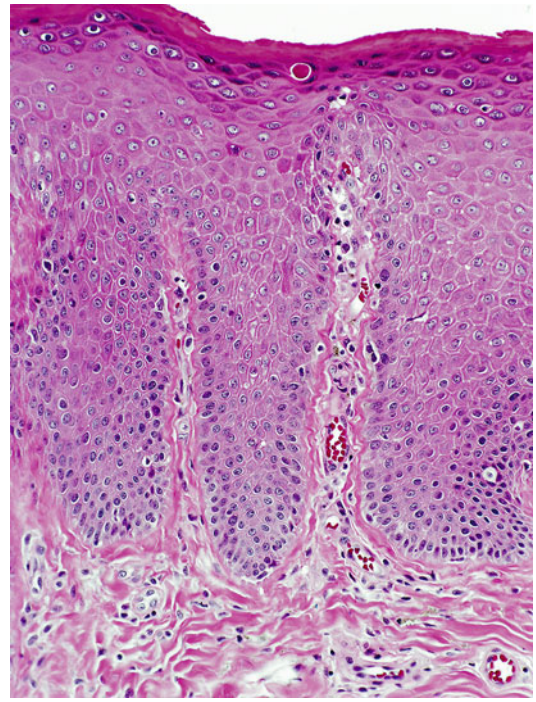


Fig. 20 LSC. The epidermis is thickened and shows focal hypergranulosis. The vertical orientation of the collagen fibers and capillaries in the papillary dermis seen here is a characteristic finding. (Reprinted with permission from Ball et al. 2015)

presence of eosinophils and neutrophils is not to be expected. Parakeratosis may be present in LSC but is generally not a prominent feature. These changes are nonspecific, and the diagnosis is usually one of exclusion.

Clinical Course and Treatment

Paradoxically, and much to the frustration of those afflicted, scratching the lesions of LSC only worsens the itch, setting up a vicious cycle which can be very difficult to control. Symptoms can be managed with topical steroids, calcineurin inhibitors, and, of course, avoidance of scratching, but recurrences are frequent.

Differential Diagnosis of Acanthotic Dermatoses of the Vulva

Clinical history will usually confirm a diagnosis of psoriasis, as most patients will have concurrent or previously diagnosed characteristic lesions elsewhere on the skin. In the absence of a clear history, or even when the patient has an established diagnosis of psoriasis, the prominent neutrophilic infiltrate seen in the disease is similar to that seen with fungal infection, and if other histologic features are at all equivocal, it is advisable to perform special stains to rule out fungal infection prior to making a diagnosis of vulvar psoriasis. The same should be done for cases of LSC showing significant inflammation, as chronic fungal infections are a common underlying cause of LSC.

Although both psoriasis and LSC are characterized by pronounced acanthosis, they are usually easily distinguished from each other. Again, a clinical history of psoriasis can be extremely helpful, but histologic features are relatively reliable in this distinction as well. The pattern of acanthosis is regular in psoriasis but irregular in LSC, and the granular layer is prominent in LSC but lost in psoriasis. In addition, thinning of the suprapapillary dermis and neutrophilic microabscesses, prominent features in psoriasis, are not present in LSC.

Table 5 Selected features of use in differentiating common acanthotic dermatoses of the vulva

	Diagnosis			
Feature	Psoriasis	LSC (primary)	LSC secondary to contact dermatitis or atopy	LSC secondary to LS
Acanthosis pattern	Regular	Irregular	Irregular	Irregular
Granular layer	Lost	Prominent	Prominent	Prominent
Concurrent involvement of extragenital skin	Yes	No	No	No
Spongiosis	No	No	Yes	No
Eosinophils present	No	No	Yes	No
Lichenoid infiltrate	No	No	No	Yes
Basal vacuolar change	No	No	No	Yes
Necrotic keratinocytes	None	Rare	Rare	Common

A more difficult problem is to determine whether LSC is of the primary or secondary type. Chronic contact dermatitis commonly evolves to LSC (see section "Allergic/Irritant Contact Dermatitis"), which may be suggested by the presence of associated spongiosis or an inflammatory infiltrate containing eosinophils. When LSC is superimposed on LS (see section "Lichen Sclerosus"), a lichenoid infiltrate or vacuolar changes at the dermo-epidermal junction may suggest the underlying diagnosis, as may the identification of hyalinization of the superficial dermis. The presence of necrotic keratinocytes, which may be numerous in LS but are scarce, if present at all, in LSC (Weyers 2015), may also be helpful in this differential. Acanthosis, hyperkeratosis, and hypergranulosis are common features in intraepithelial neoplasias of the vulva as well, but the presence of cytologic atypia, increased mitotic activity with atypical forms, and abnormal maturation patterns should distinguish them. The differential diagnosis of acanthotic dermatoses of the vulva is summarized in Table 5.

Lichenoid Pattern

The lichenoid pattern of dermatitis is characterized by a band-like infiltrate confined to the papillary dermis and basal epidermis which obscures the dermo-epidermal junction and causes focal necrosis and vacuolization of the basal keratinocytes. The lesions in this category of vulvar dermatoses may be exceptionally difficult to differentiate from one another on histologic grounds alone.

Lichen Sclerosus

LS is more common in the premenarchal and postmenopausal years and is diagnosed in an estimated 1–2% of patients in general gynecologic practice (Goldstein et al. 2005). It is currently considered to be an autoimmune condition, occurring in genetically predisposed patients (Fistarol and Itin 2013; Sherman et al. 2010). On the vulva, it involves the non-hair-bearing portions, predominantly affecting the keratinizing epithelium of the medial labia majora, interlabial sulci, labia minora, clitoris, perineum, and perianal area. The disease often begins around the clitoral hood (Fistarol and Itin 2013). Involvement may be limited to a small, single area, or may involve all of these regions in a figure-eight-shaped distribution surrounding the introitus and anus. Early lesions may appear as white papules, which typically evolve into white plaques, or as sharply demarcated and slightly elevated erythematous patches with edema. Fissuring may be seen, especially between the clitoris and urethra, in the interlabial sulci and on the perineum

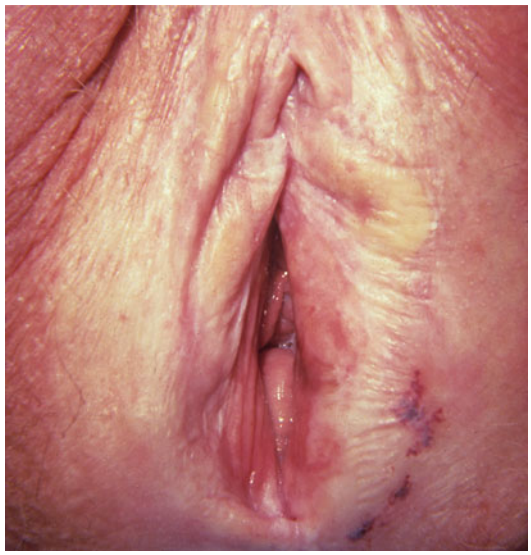


Fig. 21 The gross appearance of LS. The skin is thin, shiny, pale, and wrinkled (parchment-like), with focal ecchymosis. There is loss of distinction between the labia majora and minora

posterior to the fourchette (Fistarol and Itin 2013) as well as erosions and ecchymoses. As the lesions age, they typically become dry, hypopigmented, and finely wrinkled, an appearance likened to parchment, cellophane, or tissue paper (Fig. 21). The disease does not proceed at the same rate in all areas, so lesions of many different stages may be present in the same patient at the same time. The most common symptom in patients with intact epithelium is pruritus. Patients with associated erosions or fissures may also experience pain, dysuria, and dyspareunia. Only 9% of patients are asymptomatic (Sherman et al. 2010).

Microscopic Findings

LS was formerly known as *LS et atrophicus,* because in the classic, well-developed lesions, there is striking sclerosis in the papillary dermis and atrophy of the overlying epithelium. It has since become apparent that the microscopic findings of LS are extremely variable, and the classic atrophic, sclerotic appearance, while the easiest pattern to diagnose, is not always present. This accounts for the unique placement of LS into two categories the ISSVD classification of vulvar dermatoses (see Table 2).

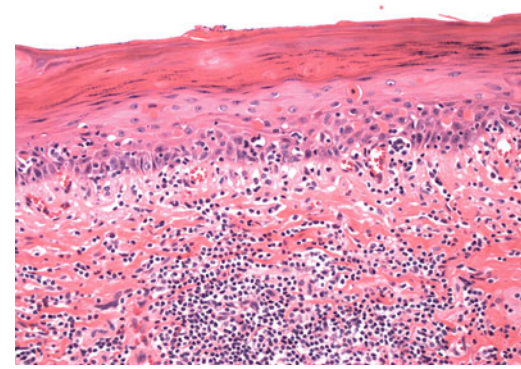


Fig. 22 LS with minimal sclerosis. The epidermis shows pronounced hyperparakeratosis, and focal dyskeratotic cells can be seen. There is a dense lymphocytic infiltrate in the dermis, as well as collagen fibrosis, with linear formations of lymphocytes between collagen fibers

Cases of LS with diminished or absent subepithelial sclerosis combined with epithelial hyperplasia rather than atrophy are not uncommon (Fig. 22), and they are significantly more difficult to distinguish from other conditions. It has long been maintained that such lesions, which show a prominent lichenoid infiltrate in the dermo-epidermal junction, with vacuolar changes and intraepidermal lymphocytes in the basal layer and little to no stromal homogenization (*lichen sclerosus sine sclerosis)*, represented early lesions, which would progress in time to more recognizable sclerotic and atrophic lesions. Yet not all cases lacking stromal homogenization necessarily represent early cases, as recent studies have found these features in lesions of long standing (Weyers 2015). Features identified in these cases which may help point to the correct diagnosis include marked thickening of the papillary dermis due to thickening of collagen fibers, lymphocytes in linear formations between the thickened fibers, and the presence of tiny foci of homogenization in the dermal papillae (Weyers 2015).

Extravasation of red blood cells in the dermis may be seen in LS regardless of the degree of sclerosis or atrophy, which accounts for the ecchymotic appearance sometimes seen. An absence of melanosomes in the keratinocytes and a disappearance of the melanocytes are also characteristics common to all LS lesions, and this lack of pigment, as well as associated edema, contributes to the white clinical appearance. In long-standing

disease, however, postinflammatory pigmentation or melanosis (see section "Postinflammatory Alterations in Pigmentation") may occur, as well as superimposed LSC (see section "Lichen Simplex Chronicus"), features which can confound the diagnosis significantly.

Clinical Course and Treatment

LS diagnosed in childhood may improve somewhat at puberty, but the majority of cases will persist into adulthood (Fistarol and Itin 2013). Untreated, adhesions and scarring from LS can lead to marked changes in the vulvar architecture, with obliteration and/or fusion of the labia minora, stenosis of the introitus, and obscuring of the clitoris. Timely and adequate therapy is imperative to prevent such changes.

LS can be controlled with treatment, and symptoms may be relieved, but complete resolution is rare. The majority of patients experience repeated relapses and remissions. Therapy using high-potency topical corticosteroids produces symptomatic relief in a majority of patients and, in some cases, complete resolution of the disease (Fistarol and Itin 2013). Close clinical follow-up is always necessary, however, regardless of response to treatment, and any area of change developing within the LS should be promptly biopsied, as there is a small but significant risk of differentiated (simplex) type vulvar intraepithelial neoplasia (VIN) and subsequent squamous cell carcinoma in postmenopausal women.

Lichen Planus

Clinical Features

LP is currently understood as an autoimmune disease, in which T-cells react against basal keratinocytes (Goldstein and Metz 2005). Half of female patients with LP are reported to have vulvar involvement (Moyal-Barracco and Wendling 2014). Most patients are between 30 and 60 years old at onset, with a peak incidence in the 50s (Cooper and Wojnarowska 2006). Vulvar pain, pruritus, dyspareunia, and burning are common symptoms, although some patients may be asymptomatic.

Three categories of lesions are described, the classical papulosquamous, the erosive-atrophic, and the hypertrophic, and patients may have more than one type simultaneously. The erosive form is the most common on the vulva, usually involving the labia minora and introitus, and appears as well-delineated, red, eroded areas. The papulosquamous form is uncommon on the vulva, and when it occurs it is usually in the setting of generalized disease, while the hypertrophic form is only very rarely seen on the vulva. Both the papulosquamous and hypertrophic forms, when present on the vulva, are usually associated with the more common erosive lesions as well.

Papulosquamous lesions present as single or multiple poorly demarcated pink, papules, rather than the well-delineated violaceous flat-topped papules typical of the lesions as described on the extragenital skin (Goldstein and Metz 2005). On the vulva, they usually involve the hair-bearing skin of the labia majora. Hypertrophic lesions present as single or multiple roughened plaques, usually in the perineal or perianal area. All types of lesion may be associated with a lacy, reticulated appearance of the surrounding epithelium, known to dermatologists as Wickham's striae.

Microscopic Findings

The histopathologic features of LP, not surprisingly, vary according to the category and location of the gross lesion. Classically, papulosquamous lesions show a sawtooth pattern of rete ridges with a wedge-shaped area of hypergranulosis, usually without hyperkeratosis. There is a dense band-like infiltrate, consisting predominantly of lymphocytes located in the upper dermis and obscuring the dermo-epidermal junction (Fig. 23). Liquefactive degeneration of the basal epithelial cells is present, and scattered necrotic keratinocytes which form eosinophilic colloid or civatte bodies, which can be seen in the basal epithelium and dropping down into the dermis. On the vulva, classic features may be less well-developed.

Hypertrophic LP is similar to the papulosquamous form, but exaggerated acanthosis is present as well, which may cause significant confusion with LSC clinically and microscopically (Moyal-Barracco and Wendling 2014).

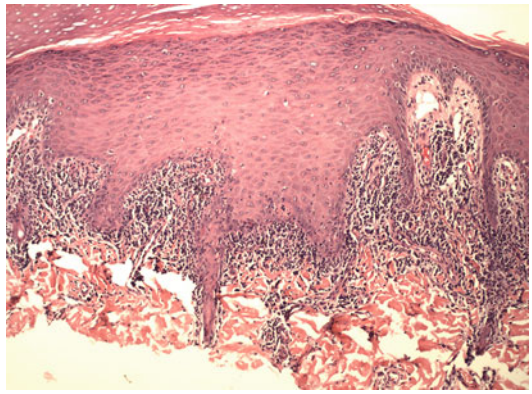


Fig. 23 LP, papulosquamous type. The lesion shows hyperkeratosis and hypergranulosis, with irregular acanthosis ("sawtooth" rete ridges) and a band-like inflammatory infiltrate of lymphocytes at the dermo-epidermal junction

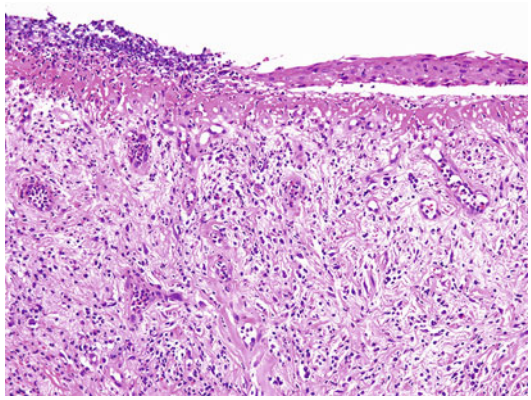


Fig. 24 LP, erosive type. The epithelium is thin and predominantly eroded, and an obvious lichenoid infiltrate is lacking. (Reprinted with permission from Ball et al. 2015)

Erosive LP (Fig. 24) frequently lacks diagnostic features on biopsy, particularly if from the central portion of the lesion where the epithelium is entirely absent. If erosive LP is suspected, it is important that the biopsy be from the edge of the eroded area. An attempt to establish a set of diagnostic criteria reached no consensus on any particular indication as being essential to diagnosis (Simpson et al. 2013) but was able to identify several clinical and histologic features considered "supportive" of the diagnosis. The clinical features include location of the eroded areas at the vaginal introitus, the presence of surrounding Wickham's striae, symptoms of pain and burning, involvement of other mucosal surfaces, and the presence of concurrent vaginal inflammation. Histologic features were the presence of a well-defined band of inflammation at the dermo-epidermal junction consisting predominantly of lymphocytes and signs of basal layer degeneration.

Clinical Course and Treatment

Like LS, untreated or unresponsive erosive LP can result in scarring and agglutination of the labia minora, severe introital and vaginal adhesions, and resultant stenosis or even obliteration of the vaginal canal (Lewis 1998). Topical corticosteroids are the first line of treatment for vulvar LP. Occasionally, other topical agents may be preferred. If topical treatments fail, systemic treatment with corticosteroids may be required (Goldstein and Metz 2005). Although treatment provides significant relief of symptoms in most patients, vulvar LP can be difficult to eradicate, particularly the erosive form. Only 9% of patients had complete resolution in one prospective study (Cooper and Wojnarowska 2006). As with LS, there is a risk of progression to differentiated VIN and squamous cell carcinoma, and close clinical follow-up is essential.

Fixed Drug Eruption

Clinical Features

The vulva is a favored site for fixed drug eruption, a recurrent type IV hypersensitivity reaction (Andreassi and Bilenchi 2014). Classically associated with pyramidone, sulfonamides, antibiotics, and Nonsteroidal anti-inflammatory drugs (NSAIDs), an increasing number of antibacterial, antifungal, psychoactive, and analgesic drugs are now recognized as potential agents. On the keratinized vulvar skin, fixed drug eruptions are usually single, erythematous, round lesions involving a distinct, clearly delineated area, which may progress to erosion. On the non-keratinized mucosa, the lesions often appear as erosions with irregular borders. The symptoms are generally mild, consisting of itching and burning.

Microscopic Features

Histologically, the lesions demonstrate spongiotic epithelium overlying a dermis with a perivascular and interstitial infiltrate of lymphocytes admixed with eosinophils and neutrophils. The inflammation may extend upward to involve the basal layer of the epithelium, causing basal vacuolar change. In the nongenital skin, the healing phase is characterized by prominent post-inflammatory pigment incontinence, but this is much less common in the vulva.

Clinical Course and Treatment

The lesions typically appear at the same place on reexposure to the responsible agent, often within minutes to hours (Ball et al. 2015). Avoidance of the responsible agent eliminates the condition.

Differential Diagnosis of Lichenoid Dermatoses of the Vulva

It can be very difficult to distinguish early LP of any type from LS without significant atrophy or sclerosis, as both are characterized by a lichenoid inflammatory infiltrate and basal degeneration. This differential diagnosis is summarized in Table 6. Clinical features may be helpful, as LS is rarely painful, only rarely involves the extragenital skin, and never involves the vagina or other mucous membranes, whereas LP is usually painful and frequently involves the extragenital skin and mucous membranes as well as the vagina. Useful histopathologic features in this differential diagnosis include the lack of melanophages in LS, which may be numerous in LP, the increased presence of lymphocytes in the epidermis in LS, and the difference in distribution of necrotic keratinocytes, which are confined to the basal layer or upper dermis in LP but extend from the basal layer up into all layers of the epidermis, sometimes forming clusters, in LS (Weyers 2015). The pattern of acanthosis, if present, may be helpful, as it is irregular in LP but usually regular in LS. Vertical columns of parakeratosis are recently described features of LS not seen in LP (Weyers 2013; Weyers 2015). Parakeratosis of any sort is uncommon in LP.

Table 6 Selected features of use to distinguish LS from LP of the vulva

	LS	LP
Vaginal involvement	No	Yes
Parakeratosis	Common, may be present in vertical columns	Rare
Extravasated red blood cells	Common	Rare
Stromal hyalinization	Common	Rare
Location of necrotic keratinocytes, if present	All layers of the epithelium, clustering may be present	Basal epidermis and upper dermis, no clusters

With blistering, erosive LP may mimic mucous membrane pemphigoid (see section "Pemphigoid"). Mucous membrane pemphigoid can be distinguished by the identification of the characteristic subepithelial blisters and the presence of abundant eosinophils in the vesicles and in the dermis. Direct immunofluorescence studies will further confirm the diagnosis, showing linear IgG and C3 deposits, which is not a feature of LP.

A lichenoid pattern may also be seen in fixed drug eruption, Stevens–Johnson syndrome, systemic lupus erythematosus, and graft versus host disease. The presence of eosinophils in the inflammatory infiltrate in fixed drug eruption helps to distinguish it from LS and LP, and the other entities are all extremely rare on the vulva and associated with other clinical findings which should establish the diagnosis. Plasma cell vulvitis may mimic a lichenoid dermatitis to a certain extent, but does not demonstrate damage to the basal epithelium, which will aid in this distinction.

Dermal Homogenization/Sclerosus Pattern

In the dermal homogenization/sclerosus pattern, the papillary dermis is thickened by the deposition

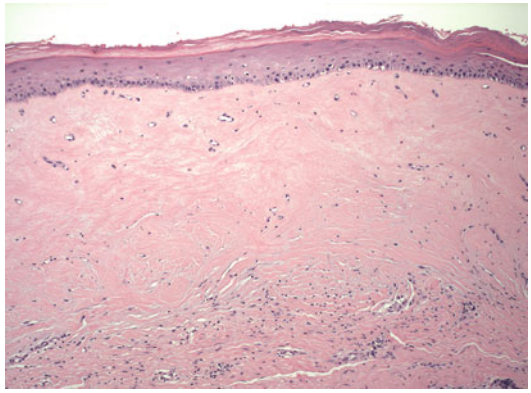


Fig. 25 LS. The well-developed lesion shows the characteristic features of thinning of the epithelium with loss of the rete ridges and a dense, homogenized layer beneath the epithelium. Deep to the homogenized tissue is the residual layer of chronic (lymphocytic) inflammation

of dense hyalinized material. LS is the only entity in this category in the ISSVD 2006 classification (see Table 2).

Clinical Features

Clinical findings are as described for the non-sclerotic type of LS.

Microscopic Findings

When the characteristic features of dermal homogenization and sclerosis are well-developed, the diagnosis is relatively straightforward. The epithelium is typically atrophic, and the rete ridges are lost. Basal vacuolization is common, and there may be sparse lymphocytes in the basal layer. Overlying hyperkeratosis may be present. The dermal homogenization is seen as a subepidermal band of paucicellular, amorphous pink hyaline material, often with edema (Fig. 25), believed to be derived from deposits of protein derived from leaky microvessels with or without inadequate venous and lymphatic drainage (van der Avoort et al. 2010). Beneath the hyaline layer is a band-like infiltrate of lymphocytes which may become less prominent as the lesion ages. As in LS without sclerosis, there may be extravasated red blood cells in the dermis, and melanocytes and melanophages are absent.

Differential Diagnosis of Sclerotic Dermatoses of the Vulva

The differential diagnosis includes morphea, which is extremely rare in the vulva and in which the dermal fibrosis extends deeper into the reticular dermis, and radiation dermatitis, in which lymphocytes are rare. Occasional neoplasms of the skin may have associated dermal sclerosis, but unless the biopsy is extremely limited, the accompanying features of malignancy should be evident.

Vesiculobullous Pattern

The vesiculobullous dermatoses are characterized by fluid-filled spaces within the epidermis or between the epidermis and the dermis, in the absence of associated acantholysis. These disorders are frequently autoimmune in nature, and immunofluorescence is a necessary tool in their evaluation. On the extragenital skin, vesiculobullous lesions are often intact, tense fluid-filled blisters, but on the vulva local conditions are such that most lesions are rapidly ruptured and collapsed, and more likely to present as erosions, which may confound the clinical impression.

Pemphigoid

Clinical Features

Bullous pemphigoid, the most common of the autoimmune blistering diseases, involves the skin and, in a minority of patients, the mucous membranes. A significant number of patients have associated neurologic disease (Schiavo et al. 2013). Mucous membrane pemphigoid, formerly known as cicatricial pemphigoid, is a similar disease, but involves the mucous membranes exclusively. Both are caused by autoantibodies, sometimes developed in the context of a drug reaction, viral infection, or other inducing factor, to the components of hemidesmosomes and to type VII collagen, leading to loss of adhesion between the basal epithelium and the basement membrane.

Although bullous pemphigoid is significantly more common than mucous membrane pemphigoid, vulvar involvement is more common