Atlas of Mohs and Frozen Section Cutaneous Pathology

Second Edition

Michael B. Morgan
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Dedication
To Kerry, Poochie, and Bozie for your unconditional love and acceptance of the time and effort I have spent away from you in this endeavor.
Michael B. Morgan, MD

To Glicia and James, thank you for your love and encouragement.
James M. Spencer, MD

I would like to thank my mentor and friend in medical school, Robert Bookmyer, MD, from my dermatology training at the University of Chicago. I would like to thank Alan Lorincz, MD, for inspiring me to think creatively; Maria Medenica, MD, and David Fretzin, MD, for dermatopathology; and Keyoumaris Soltani, MD, for dermatological surgery. I also want to thank Frederick Mohs, MD, for being so generous and sharing his expertise with me. Most importantly, I want to thank my wife Sue and my children John, Sarah, Amy, and Gregory for their support and encouragement.
John R. Hamill, Jr. MD

To my mother, Mary Barber, who has always been my inspiration and to my husband, Christopher, for his unwavering love and support.
Rebecca Thornhill, MD

Preface

This atlas is intended for practitioners in the fields of dermatologic surgery including Mohs cutaneous surgeons, pathologists who examine frozen section specimens derived from the skin, and dermatopathologists. This book will serve as a reference pictorial atlas detailing both common and challenging cutaneous neoplasms. It will also serve as a review for physicians-in-training preparing for certifying examinations in the fields of dermatology, dermatologic surgery, Mohs surgery, pathology, and dermatopathology.

The central theme of the atlas entails the microscopic analysis, diagnosis, and discrimination of common and problematic cutaneous neoplasms as encountered by the dermatologist, cutaneous surgeon, or pathologist employing the frozen section technique. The book includes coverage of (1) microscopic anatomy of the various cutaneous and mucosal sites of the body; (2) diagnosis of basic/routine dermatologic entities including basal cell carcinoma and its variants as well as squamous cell carcinoma and its variants; (3) the discrimination of these foregoing neoplasms from benign epidermal-derived or adnexal-derived neoplasms; (4) diagnosis and distinction of rare and/or deadly neoplasms from benign entities such as dermatofibrosarcoma protuberans and merkel cell carcinoma; (5) troubleshooting and dealing with quality control of the frozen section technique including cutting and staining; (6) new techniques including immunohistochemistry and molecular analysis.

The underlying premise of this atlas is to provide its reader with a single reference atlas dealing with the frozen section microscopic diagnosis of cutaneous neoplasms. As these malignant entities are capable of presenting in a variety of microscopic guises potentially confused with benign mimics or in a subtle fashion easily missed by the examiner, it is important that pathologists or clinicians who interpret their own biopsies are apprised of this risk.

This book should provide a shelf reference for dermatologic surgeons, Mohs cutaneous surgeons, pathologists who perform frozen section analysis of cutaneous specimens, and dermatopathologists. This book should also serve as a potential study source for dermatologists, pathologists, and dermatopathologists preparing for board examinations.

Tampa, FL, USA — Michael B. Morgan, MD
Saint Petersburg, FL, USA — James M. Spencer, MD
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Prologue

Skin cancer has reached epidemic proportions in the United States, and there is no evidence that this trend will decrease any time soon. Basal cell and squamous cell carcinomas, collectively referred to as nonmelanoma skin cancer, make up the vast majority of the estimated 1.5 million skin cancers seen annually in this country. There are many ways nonmelanoma skin cancer may be treated, ranging from topical medications for early thin tumors, destructive techniques such as cryosurgery or curettage and electrodessication, radiation therapy, surgical excision, and lastly excision utilizing the Mohs technique. Of all these techniques, the highest cure rates currently possible are with the Mohs technique, which relies on optimal preparation and interpretation of frozen sections. Therefore, frozen section analysis has become the gold standard for skin cancer therapy.

When surgical excision is chosen as the treatment, frozen section analysis allows histologic information to become part of therapy, rather than preceding therapy (in the case of a biopsy) or confirming an already finished procedure (permanent sections read days after the surgery is over). Frozen sections may be utilized to sample a portion of a conventional surgical excision, or they may be used to examine all the exterior surface of the excised tumor during the Mohs technique. Cure rates with either conventional surgery or the Mohs technique can only be as good as the quality and interpretation of the frozen sections.

Frozen section analysis is fundamentally different than permanent sections. Details from individual cells are difficult to assess, and pattern recognition becomes more important. Traditional permanent sections have vertical cuts, and thus structures of the skin are seen vertically oriented. Slides prepared as part of the Mohs technique produce sections with horizontal and tangential cuts on the same slide, and thus familiar structures are now altered in their appearance. Experience in reading vertically oriented permanent sections does not translate to expertise in reading frozen sections. In my opinion, the most difficult part in mastering Mohs surgery is not the excision or reconstruction, but rather developing expertise in reading horizontally and tangentially oriented frozen sections.

It is our hope that this book provides a scholarly reference text to the student of frozen sections for skin cancer therapy. The authors include pathologists and dermatologists practicing Mohs surgery. Mike Morgan, a dermatopathologist, has been the lead author and editor who has carried the lion's share of getting this book done and deserves our thanks. Hopefully, dermatopathologists reading frozen sections, as well as practicing Mohs surgeons, will find this text a useful and handy reference to keep in the lab.

Tampa, FL, USA — James M. Spencer, MD

The Early Days of Mohs Surgery

Mohs surgery is an extremely effective method for eradicating skin cancers. The unique feature of the technique is that it incorporates instant pathology while the patient waits. The value of the laboratory in producing frozen sections within a short period of time enables the physician to determine if all of the tumor has been removed. Upon microscopic examination of excised tissue, the physician is able to pinpoint its exact location on the patient.

Initially, the availability of cryostats was limited, and the freezing microtome stage was fed by a supply of CO_2 gas that was stored in large containers. The gas was allowed to pass through narrow tubing to reach the microtome stage and freeze the tissue. The CO_2 containers were often large and bulky, requiring substantial storage space. Furthermore, the dependence on timely deliveries of the CO_2 led to many inconveniences in attempting to process the tissue obtained from Mohs surgery. Shortly after, a new type of microtome was developed utilizing an electrical unit that provided a supply of cold air to freeze the specimen on the stage. In subsequent years, cryostats such as Leica became more practical and affordable and are among the most used in Mohs surgery practices today.

Before the 1970s, the Mohs technique incorporated the application of a zinc chloride paste and was thus known as microscopically controlled chemosurgery. The final patented formula contained 45% zinc chloride by weight, with 40 g of stibnite antimony, 10 g of bloodroot (*Sanguinaria canadensis),* and a 34.5 mL zinc chloride saturated solution. The stibnite antimony acted as a granular support material, and the bloodroot kept the zinc chloride in suspension so that it could freely move between the particles, yet not settle to the bottom. The product was not FDA approved and was prepared by the University of Wisconsin pharmacy, where at the time it could only be purchased under the authority of Fred Mohs.

The zinc chloride paste was effective in fixing the tissue in situ. It was applied in a thin layer over the involved area and could not penetrate the skin unless keratin was removed. This was accomplished using dichloroacetic acid. It turned the affective area white due to precipitation of the proteins in the epidermis. Using the zinc chloride paste, Dr. Mohs created Z squares in which he impregnated a piece of gauze with the paste and cut into 1 cm^2 pieces. Theses gauze pieces were then applied to the Mohs defect site to prevent the area from drying out. This entire process came to be known as the fixed tissue technique.

Although Dr. Mohs had published work on the fresh tissue technique in the late 1950s, it was not until the mid-1970s that it became the favored method in Mohs surgery. In 1970, Dr. Tromovitch presented a paper at a chemosurgery meeting, reporting a 99% cure rate with close to a 5-year follow-up. The advantage of using the fresh tissue technique was that many stages of Mohs surgery could be performed in one day, and the defect could be repaired immediately following completion of the surgery. Today, there are some Mohs surgeons who continue to use the zinc chloride paste to treat malignant melanoma. They believe that the paste plays a role in killing melanocytes; however, this has not yet been substantiated. Therefore, the fresh frozen technique has become the preferred technique in the vast majority of Mohs surgery practices.

In the early days, the favorite stain for basal cell carcinoma was toluidine blue. It caused the mucopolysaccharides to stain purple revealing the presence of tumor cells. The use of toluidine blue was less popular for squamous cell carcinoma as it was more difficult to differentiate

tumor from normal tissue. Toluidine blue was taken off the market in its initial formulation as it was found to be carcinogenic at higher concentrations. Hematoxylin and eosin became the standard for both squamous cell and basal cell carcinomas as well as various tumors for which Mohs surgery is utilized as treatment. The toluidine blue used today is at a much lower concentration and is preferred by many Mohs surgeons for visualizing basal cell carcinoma. However, its perceived advantage over hematoxylin and eosin is simply a matter of personal choice.

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Part I

Introduction

Mohs and Frozen Section Overview

1

Michael B. Morgan and Terri Bowland

The evaluation of frozen section prepared tissues derived from the skin constitutes a burgeoning area of hospital- and outpatient-based pathology practice. Frozen section cutaneous pathology encompasses a diverse array of techniques for preparing the skin specimen and incorporates a variety of diagnostic methodologies. This book will principally address the histologic interpretation of the various cutaneous neoplasms encountered with the Mohs micrographic frozen method and traditional fresh-frozen pathology. Unusual diagnostic applications of frozen sections such as frozen section immunopathology and unconventional topics such as perineural pathology and quality assurance with technique trouble-shooting will also be covered.

Understanding that the vast majority of cutaneous neoplasms can be successfully removed in the outpatient setting without the aid of frozen section examination or treated without examination of removed tissues (e.g., photodynamic therapy, topical immune response agents (Imiquimod) or palliative measures (e.g., radiotherapy or intralesional chemotherapy), the principal discussion will revolve around the frozen-section determination of both the more common non-melanoma skin cancers, unusual malignancies of the skin (e.g., merkel cell carcinoma), simulants of cutaneous cancer, as well as discuss the important differential diagnoses and pitfalls that arise in the preparation and interpretation of these specimens. The first chapters will entail an in-depth examination of the normal epithelium, dermis and subcutaneous fat. Important age-related and/or benign degenerative changes such as solar elastosis will be discussed. Each of the topics to be considered will be preceded by a brief synopsis or *précis* of the entity entailing its epidemiologic, definitional, pathogenic, clinical and pathologic features. This will be followed by a traditional text document pertaining to the précis and finally, high-quality color photomicrographs taken at low, medium and high powers of magnification. The photomicrographs will be prepared from frozen section material and will be presented in a contrasting format with the most important differential diagnosis presented adjacent to the topic headings. The margins of each photo will contain the most important diagnostic points useful in distinguishing the entity. Each chapter will be followed by a concise bibliography.

Indications for Frozen Sections of the Skin

The principal application of frozen section consultation is to assure the complete removal of a non-melanoma skin carcinoma (NMSC). The goal is not only to completely remove the abnormal tissue but to assure that as minimal amount of normal tissue is removed for cosmetic or functional purposes. The functional concerns entail preservation of as much of the normal anatomy as possible in highly-functional tissues such as the peri-ocular adnexae, eyelids and around the mouth or nares. In the removal of larger specimens that require complicated closures with the aid of tissue flaps or grafts, assurance of negative tumor margins is essential. Frozen section examination is also commonly employed in circumstances where the tumor has recurred or excessive post-operative scarring or radiotherapy complicates the clinical determination of tumor borders. The final indications involve the determination of various cutaneous dermatoses such as toxic epidermal necrolysis versus the staphylococcal scalded skin syndrome. As both conditions show considerable clinical overlap, portend a grave prognosis and involve vastly different modes of therapy, rapid frozen section determination between these entities can become necessary.

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Histologic Prerequisites to Frozen Section Evaluation

Several practices should be adopted prior to frozen section examination of the skin. One of the most important exercises to routinely employ is the pre-procedural review of permanent tissue sections obtained by prior biopsy of the lesion scheduled to be removed. In some instances, the original interpretation rendered is in error or may involve histologic subtleties usefully remembered in the interpretation of the subsequent specimen. Familiarity with the normal histology and its key variations is assumed. Dermatopathology text review, literature search and/or web image review can also be resorted to with planned removal of unusual entities. Among the more varied pathologic nuances potentially encountered that pose considerable challenge during frozen section interpretation are morpheaform basal cell carcinoma, microcystic adnexal carcinoma, dermatofibrosarcoma protuberans and simulants of malignancy such as psuedoepitheliomatous hyperplasia, basaloid follicular hamartoma and dense/obscuring inflammatory infiltrates, which will be subsequently discussed.

Handling of the Specimen/Frozen Technique

Adequate preparation of the glass slides to be examined and the tissue chucks to be utilized are prerequisite to the handling of the skin specimen. Glass slides should be prepared with adequate patient identification, employing alcohol fast labeling, typically with leaded pencil marking. If possible, a technique employing a redundant patient identification mechanism, i.e., patient name and surgical or operative number should be considered. Cryostat tissue section chucks should be mounted with OCT embedding compound prior to tissue receipt. Once frozen, the OCT should be planned to ensure a flattened surface. This can be accomplished by simply rubbing the surface of the frozen chucks over a clean, firm, smooth surface. The undersurface of the chucks may be labeled with a colored wax pencil or pencil-lead.

Upon receipt of the specimen, assurance should be made as to the origin and correct identification of the specimen, ascertained by matching the specimen jar or sample container with the requisition form. The time of specimen receipt should also be recorded for quality assurance and turnaround-time determinations. Special attention should be given to the size, shape and particularly identifying marks, contrasting inks or suture ties orientating the specimen. The anatomic location, dimensions (three planes), the number of visible lesions, their dimension, surface attributes (e.g., keratotic, ulcerated, etc.), color of the lesion and orientating features should also be recorded. Anatomic orientation should be maintained if possible in the preparation of the specimen. Orientation may be arbitrarily assigned to clock positions (e.g., 12 o'clock) representing either an anatomically cephalad or superior orientation or corresponding to a tip of an ellipse and recorded with the aid of a diagram. Generally, skin specimens are configured in an elliptical or oval silhouette as to allow cosmetically-acceptable closure of the wound (Figs. 1.1 and 1.2). Rarely, triangular (often from the ear or lip) or oblong specimens will be received pending anatomic considerations or the extent of tumor extension. Typically, oval or elliptical specimens measuring less than 1.0 cm in length can be sectioned and submitted entirely in a single cassette. Multiple blocks may need to be prepared for larger specimens.

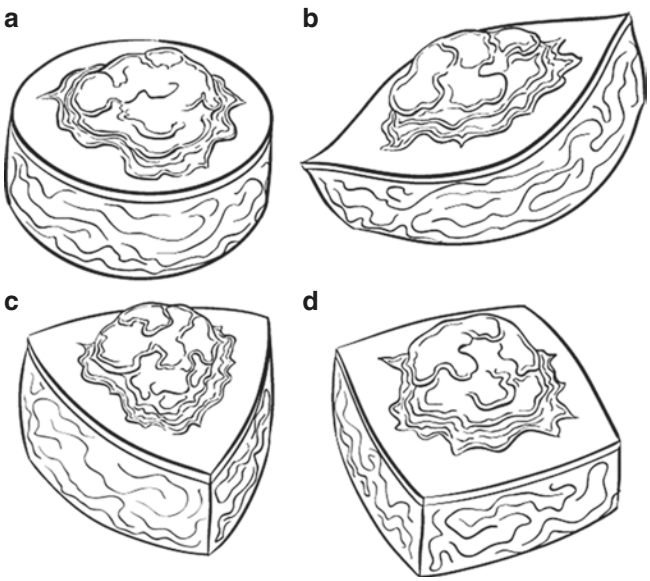

Fig. 1.1 Round specimens (**a**) represent a minority of specimens submitted for frozen sections. An ellipse (**b**) is the most common with the tips taken to assure cosmetic closure of the defect. Triangular shaped (**c**) and rhomboid-shaped (**d**) specimens are most often removed in preparation for closing the defect with a local skin flap

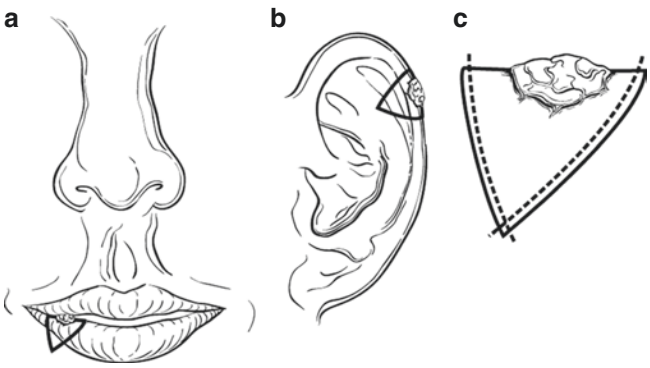

Fig. 1.2 Wedge-shaped biopsies are obtained from free margin anatomic locations such as the lip (**a**), or ear (**b**) Sections are cut parallel to the margins and embedded on edge (**c**)

Orientation

Specimens should be received with accompanying orientation marks including a notch, contrasting edge or surface ink(s) and/or sutures (Fig. 1.3). The latter is preferred, and usually, a single suture is all that is necessary. An anatomically oriented sketch or diagram corresponding to the designated orientation is preferable as well. In most instances, the suture or mark may be assigned if not previously by the surgeon, to 12 o'clock with the remaining positions corresponding to a clock-face. Complicated resections may require in situ examination or clinical photographs of the outlined specimen margins prior to removal by the pathologist. Sutures should be tied off in a loose loop configuration to assure complete and efficacious removal of the suture material. Retained suture within the specimen or inadvertent slicing of the excision by the pathologist may follow tight knotting of the suture to the resected specimen.

Inking

Prior to cutting of the specimen, all surgical margins of the tissue should be painted with contrasting inks to assure microscopic delineation of orientation and tumor extent (Fig. 1.4). The ink can be applied with the aid of a toothpick or similarly configured wooden or plastic applicator to the surgical margins of the specimen. To assure steadfast ink adherence to the specimen, thorough drying of the specimen edges with a paper towel should precede ink application.

Typically, contrasting inks of red and blue are employed for the peripheral margins and black for the base of the specimen. Additional inks may be applied to assess tips or oblong peripheral margins. Excess ink should be blotted from the surface of the painted specimen prior to each additional ink application. Following inking, the specimen is prepared for cutting.

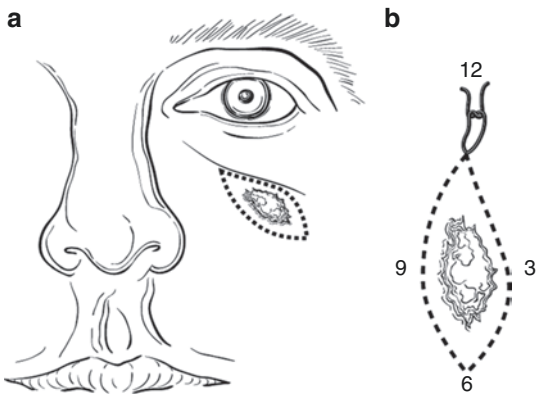

Fig. 1.3 A suture placed at a designated point (e.g., 12 o'clock) is the most common way for the surgeon to orient the specimen

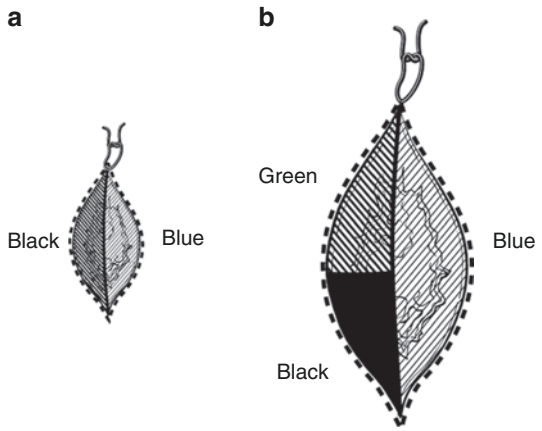

Fig. 1.4 Inking an ellipse. A small ellipse (less than 1 cm) should be painted with at least two contrasting ink colors (**a**). Larger ellipses (**b**) can be painted with at least three inks

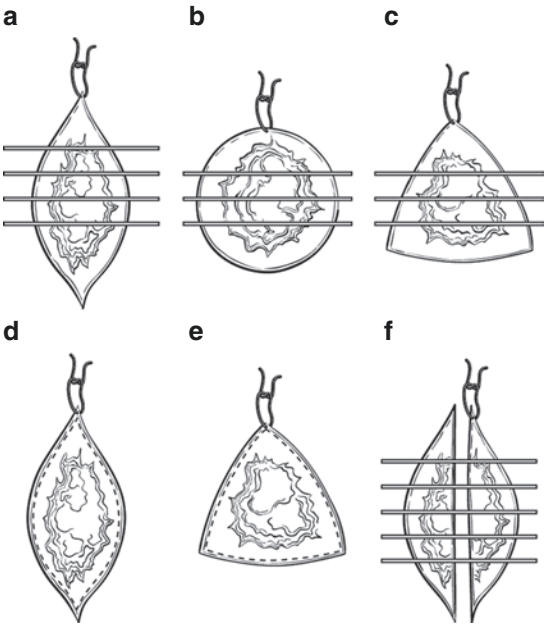

Fig. 1.5 Recommended ways to cut specimens. In each instance smaller (less than 3 cm) elliptical (**a**), round (**b**), or triangular (**c**) specimens single side is painted with a single or preferably two contrasting inks corresponding to the 12 o'clock to 3 o'clock and 3 o'clock to 6 o'clock margins, respectively, with the entire 6 to 12 o'clock margin painted in a third color. The base is typically painted in black. The specimens are bread-loafed along the short axis. Larger elliptical specimens (**d**) eliptical (**e**), or triangular (**f**) can be prepared with parallel sections taken along the surgical margins

Cutting the Specimen

Typically, the specimen is bread-loafed perpendicularly to the long axis at nickel-thick intervals as to assess the peripheral extent of the tumor microscopically (Fig. 1.5). Exceptions to this rule exist however. Larger specimens (greater than 3 cm in length) may be cut parallel to the

surgical margins and embedded in different cassettes. Wedge or triangular-shaped specimens should be handled as follows: Each of the mucosal or cutaneous surgical margins should be assessed by taking parallel sections along the surgical margins to the apex with the remainder of the specimen bread-loafed entirely.

Embedding

Embedding of the cut-tissue specimens is of particular concern. Anatomic orientation should be maintained for all specimens with the epidermal surface of each specimen arranged to first meet the knife edge upon sectioning (Fig. 1.6). Generally, no more than four specimens should be placed upon a single block as it is difficult to assure complete and uniform facing of the block with each of the cut specimens when this number is exceeded. The tips of elliptical or rhomboid shaped specimens may be deferred to permanents as they rarely possess carcinoma. Typically, the true surgical margin in parallel sections is mounted deep to assure its preservation with sectioning. Cryostat sections should be approximately 4 microns thick, and efforts should be made to ensure that the tissue sections are not folded and that immediate fixative immersion is performed once this tissue is firmly affixed to the slide. Sections should not be obtained for staining until the tissue is uniformly frozen and completely surrounded by OCT medium. Re-excision specimens may occasionally pose some quandary in preparation and cutting. Typically, wider excisions will incorporate a central defect with an intact base allowing uniform breadloafed sections. Occasionally, the specimen will possess a through-and-through central defect. Care must be exercised in properly orienting the halfed peripheral portions obtained from the central defect area.

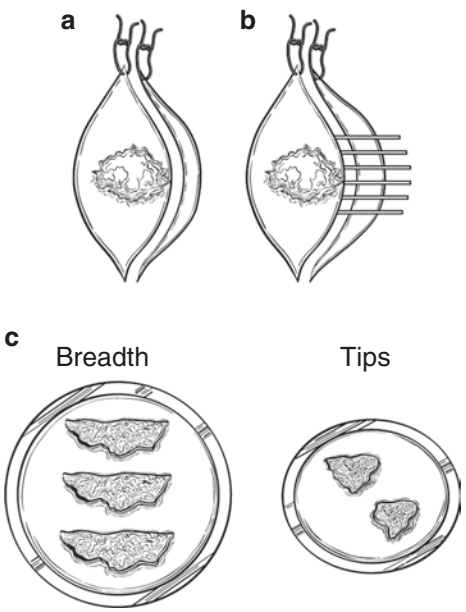

Fig. 1.6 Placing tissue in the block maintaining orientation. The pieces are placed sequentially, so that if a positive margin is obtained, the site of involvement can be determined (**a** and **b**). Peripheral portions of central area should be placed in register with flanking sections (**c**)

Mohs Technique

The Mohs technique was developed by Dr. Frederic Mohs in Wisconsin over 50 years ago as a means of extirpating nonmelanoma skin cancer among patients who either failed traditional surgical means of removal or were deemed potentially inoperable on the basis of the tumor dimensions or anatomic location. The technique incorporates an alternative means for securing and preparing the tissue specimens for rapid histologic interpretation. The principal difference lies in how the tissue sections are cut prior to interpretation. Due to the emphasis upon conserving as much normal tissue as possible, orientation of the specimen is at a premium and is accomplished with the aid of meticulous use of color coordinated sketches. The first specimen taken termed level one is first examined to confirm a tissue diagnosis followed by the removal of successively wider slivers of involved-margin tissues termed levels. The first level is typically excised round with a 45° angle to assure that the specimen can be easily manipulated and is typically no thicker than 4 millimeters in thickness. In such fashion, the epithelium is vertically oriented with the dermis and subcutaneous fat oriented in a horizontal fashion allowing for the epithelium to be circumferentially visualized with the dermis. The process can be imagined with the aid of an orange (Figs. 1.7–1.10).

Sections so prepared will show the deep margin with the entire peripheral aspect of the epithelium. The successive

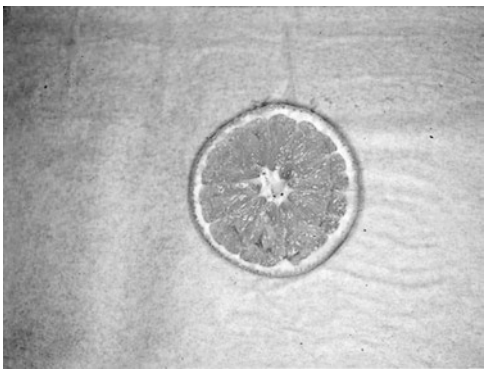

Fig. 1.7 The meaty substance of the orange representing the tumor/dermis and the peel the external margin

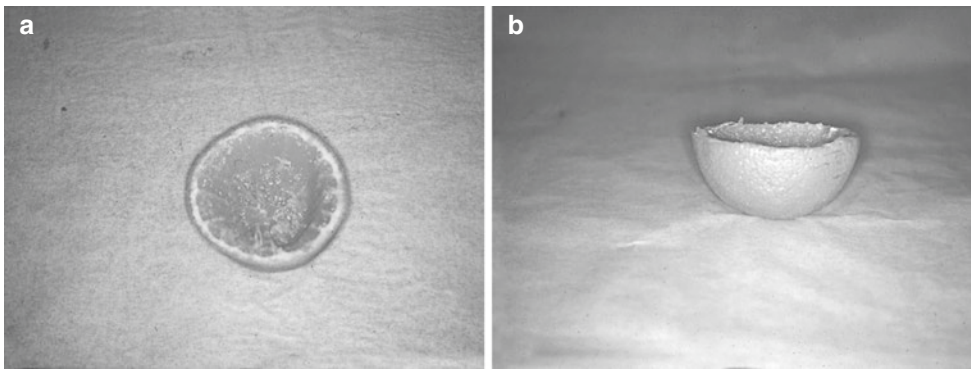

Fig. 1.8(a and b) The tumor (orange) is debulked with a curette and then beveled

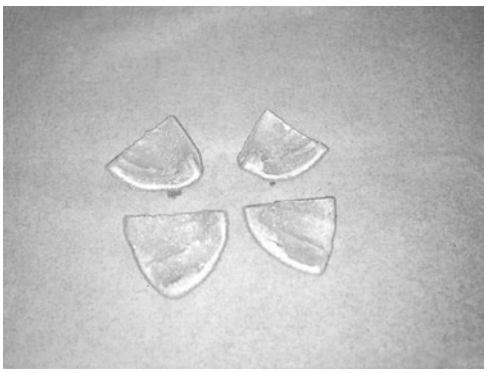

Fig. 1.9 Notice how the peel is unfolded so that 100% of the exterior surface is examined in a single plane following sectioning

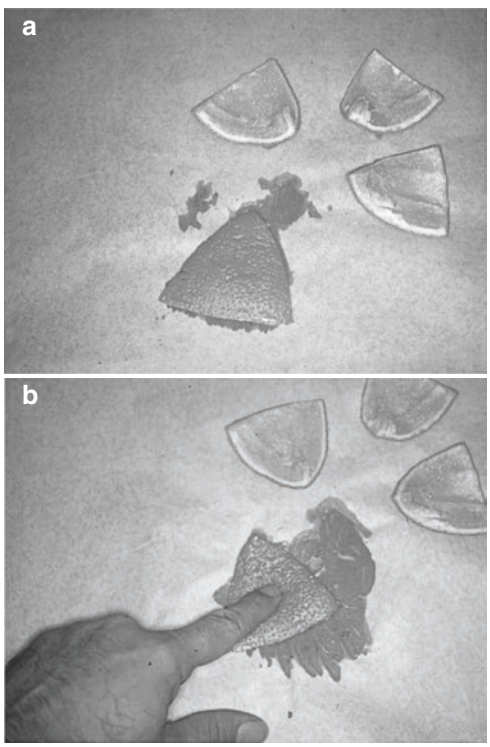

Fig. 1.10(a and b) Next, the specimen is placed deep-side down upon a cold bar or chuck without OCT, and the surface edges are pushed down to allow adherence to the cold bar forming a crowning-contact of the entire epidermal margin circumference

levels are divided into roughly equal color delineated quadrants or as slivers if only focal margin positivity is encountered, each examined separately following tissue freezing and staining. The specimens are prepared for examination in a radial fashion in which the soft tissue margins are preferentially examined in a successive manner to permit the sparing of as much normal tissue as possible. Unlike traditional bread-loafing of the skin specimen, this technique involves successive longitudinal cuts emanating from the epicenter of the tumor basin. This technique is ideally suited for non-melanoma cutaneous carcinomas such as basal cell carcinoma and squamous cell carcinoma or low-grade cutaneous sarcomas such as atypical fibroxanthoma or dermatofibrosarcoma protuberans that represent low-grade malignancies that tend to recur locally, rarely metastasize and involve little risk to the patient should a narrow margin of resection in an effort to preserve normal tissue result in incomplete removal and recurrence of the original tumor. The application of this technique or traditional frozen sectioning to high grade malignancies such as merkel cell carcinoma or melanoma constitutes a more controversial area as these tumors possess a high propensity to metastasize and if allowed to recur and or remain incompletely removed following initial excision, are associated with a poorer prognosis. The Mohs technique is typically employed in the outpatient setting by surgeons specially trained in this technique as dermatologists or plastic/ENT surgeons. The principal utilities of this technique include the efficiency of the technique as a single physician is involved in the removal and interpretation of the specimen and that it can be performed in a outpatient setting. The principal disadvantage of this technique is the time involved in examination and preparation of the tissues compared to routine outpatient-based excision as well as the expertise required by the operator. The success rate of this method as determined by the recurrence rate is at least comparable to traditional frozen-section methods with some series showing a superior recurrence rate.

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Quality Assurance

2

Dennis H. Nguyen, Daniel M. Siegel, Deborah Zell, and Richard Spallone

The outcome of Mohs micrographic surgery relies heavily on the abilities of the histotechnician. The duties of the Mohs histotechnician require more precision than those of the general histotechnician. Central to this are the understanding and skill set required in preparing sections so the surgeon can assess the entire peripheral margin. Mohs histotechnology training can take place at standard histotechnology education programs or can be learned on the job. It is the experience of the authors that most people who have been trained to cut routine histopathology can be trained to cut Mohs sections.

This chapter will review the Mohs histotechnology process and the salient aspects of maintaining high quality sections.

Tissue Preparation

The work of the histotechnician begins at the point the surgeon harvests the tissue. The surgeon has many ways of marking the tissue for orientation and cutting into discrete tissue blocks. The most common methodology is to create extended hash marks at each of the points where the tissue will be cut. Most frequently, a nick is created at the six and 12 o'clock or three and nine o'clock points in anticipation of a bisected specimen. Some individuals will place additional hash marks on one half of a specimen to create asymmetry if they do not have a meticulous way of guaranteeing the tissue will not be rotated from the time it leaves the patient to the time it is brought into the laboratory. A double hash mark at one point can also be employed to serve the same purpose. On very small specimens, as will be discussed below, the specimen can be maintained as one piece with a "pacman" or butterfly configuration.

Our surgeons dissect and gross the specimen in the procedure room, though this is an issue of personal preference. Some feel grossing by the histotechnician under magnified light allows the technician to prepare specimens optimally for cutting. Regardless, one should try to create the least number of blocks for a given specimen. In creating tissue blocks, each cut edge represents an area of thickness that can rotate or roll toward or away from the blade. In principle and in practice, each edge represents an additive potential for false positives or false negatives. Thus, the optimal Mohs stage is a very thin one that is cut into as few pieces as possible [1].

In our practice, pre-printed diagrams of the face and body are used for mapping. The mapping itself is done by the surgeon with the histotechnician marking in the dyed areas. A drawn representation of the initial specimen is made by the surgeon, with the orientation and size maintained as best as possible. A map that is drawn true to the tissue specimen allows the surgeon to easily superimpose persistent areas of tumor on the slide to the map and, ultimately, to the surgical site (Fig. 2.1).

A variety of commercial dyes is available for the inking of specimens. The Davidson Dye System and the Delasco tissue stains are popular choices among many Mohs labs and provides a wide variety of color options. Classically, Dr. Mohs used mercurichrome as his red dye and concentrated laundry bluing as his blue dye. While choice of dye is one of personal preference, it is important that the dye be applied sparingly as dye bleeding from one area to another may lead to confusion and inability to differentiate how the specimen should be correlated to the surgical site. In that unfortunate situation, if persistent tumor is noted, one is obligated to treat both the area felt to be positive and its mirror image so that the chance of leaving tumor behind is eliminated. In our

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Fig. 2.1 Areas of positive involvement are marked on the map and can be correlated closely to the cut section and surgical site

practice, inking is typically done by the histotechnician, though in some practices it is done by the surgeon.

Some specimens, such as those that are cut thickly or with tall 90° edges, do not lie flat on their own. In these cases, relaxing incisions can be used to facilitate the complete flattening of the tissue and its marginal surface. These incisions on the non-marginal surface are cut partially through the thickness of the specimen, taking special care not to cut through to the marginal aspect. These incisions can take on several configurations including: a cross-hatch pattern, or concentric cuts parallel to the epidermal margin and transected by radial incisions [2]. Debulking of the central portion of the specimen can also facilitate flattening. These techniques can be performed in-vivo or ex-vivo and work well on most soft tissues. Incisions and debulking performed in-vivo minimize the risk of tissue margin disruption that can occur artificially in the lab. Relaxing incisions do not work as well on cartilage, however. It is our experience that slides prepared with neither albumin nor commercially available charged slides significantly help cartilage stay in place. The most useful way to keep cartilage in the final tissue sections is to take the stage so as to maintain the cartilage's attachment to soft tissue. This tissue acts as a tether or hinge so that the cartilage stays in place and will not float or "chunk" away during sectioning and staining. Special care must be taken to minimize agitation of the tissue during the staining process to keep it in place.

Sectioning

There are many commercially available cryostats, with the majority today manufactured by Leica, TBS and Microm (Zeiss). The choice of cryostat is one of personal preference, particularly as it relates to the important features of tissue advancement and tissue cutting. It is the experience of the authors that automated tissue advancement can be a significant timesaver. However, automatic cutting of tissue for frozen sections does not allow for the precise control that the manual hand wheel offers in working with difficult specimens, though this again is an issue of personal preference.

Temperature

The ambient environment plays an important role in the cutting of tissue. High ambient temperatures can make it difficult to maintain cold temperatures in the cryostat. It is not impractical to have separate air conditioning controls for the Mohs laboratory to maintain a cooler temperature. High humidity in the room can lead to curling of specimens. Condensation that accumulates in humid conditions results in ice crystal formation that can cause cracks and fragments as the tissue is being cut.

Cutting temperature within the cryostat of approximately −24° to −26° C is ideal for most soft tissue. One exception is fat, which tends to cut better at colder temperatures of −28° to −32°. If the histotechnician cannot cool the tissue down by either using an external freeze spray or liquid nitrogen, another option is to cut double- or triple-thick sections. This will likely make some epidermal features unreadable, but will give intact and readable fatty tissue.

Embedding

Many methods are employed in the critical stage of embedding tissue for Mohs sectioning. Regardless of the method, the clear objective is to embed a complete and flattened marginal plane on the mounting disc that will facilitate level sectioning (Fig. 2.2).

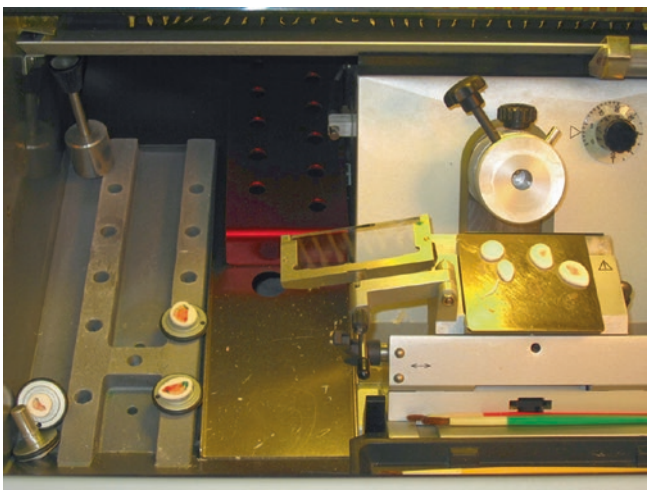

Fig. 2.2 Here the tissue is flattened directly onto the stage as embedding media is applied. Once complete, mounting discs are placed on the freeze bar (as seen on the *left*) before sectioning

In the *direct or floating technique*, embedding media is placed on a mounting disc. The specimen, with the marginal surface facing outward, is embedded into the semi-solid media. Care is taken to tease the epidermal edges up to create a level plane. A glass slide or heat extractor can be laid across the face to facilitate this. This method has lost popularity with the wider use of heat extractors and direct use of the freeze bar.

In contrast with the *heat extractor method*, the marginal aspect of the specimen is placed down directly onto the heat extractor. The specimen is manipulated to lie flat before embedding media is applied. Once sufficiently frozen, the specimen is flipped and placed on the mounting disc in a level manner, and allowed to freeze. The frozen specimen may not come easily off the heat extractor, and in these cases, many recommend that Teflon tape be applied to the face of the heat extractor before the tissue is first applied to prevent sticking. The heat extractor method has the advantage that the extractor can be taken out of the crytostat, and tissue manipulation can be done comfortably in open space. The *freeze bar method* is similar in principle to the heat extractor method, except that the freeze bar is a fixed area in the cryostat, and all work is accomplished within those confines.

With the *glass slide technique*, the marginal aspect of the specimen is laid down flat on a glass slide. The glass slide's transparency allows the specimen to be teased while the marginal surface is directly visualized. Once this is achieved, the slide is placed on the freeze bar, and embedding media is placed atop the specimen. Embedding media is placed across the face of the mounting disc. Once they both reach a near frozen state, the slide is flipped and placed in a level manner atop the mounting disc. Warmth from the histotechnician's fingers or thenar eminence will release the specimen from the glass slide and allow level mounting on the mounting disk.

Freezing should be done as quickly as possible to minimize ice crystal formation. The Miami special clamps were adapted and devised, in part, to facilitate embedding in the hot and humid environs of Florida [3] (Fig. 2.3).

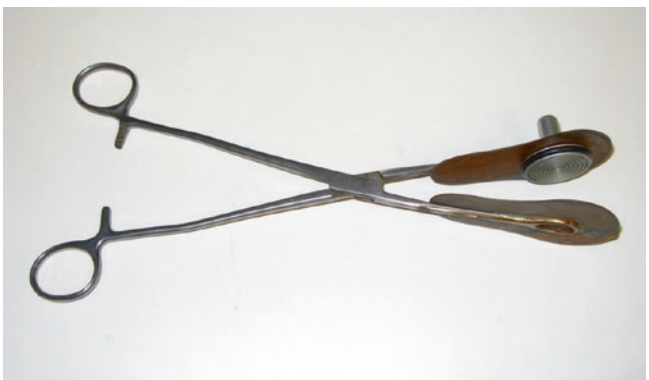

Fig. 2.3 Modified obstetric clamps, shown with mounting disc inserted

These modified obstetric clamps allow the specimen to be secured onto a glass slide while being immersed in liquid nitrogen for quick freezing. A hole in one plate of the clamp allows a mounting disc to be introduced and clamped onto the specimen. This apparatus works very well for small specimens, though for larger specimens, the specimen cannot achieve true leveling due to the angle and pivot of the clamp's plates.

Cutting

Cutting blades are generally categorized as permanent or disposable and may be specific to the type of cryostat used. Permanent blades may be sharper than disposable blades and can be resharpened as needed. We use disposable blades which are safe, efficacious and cost-effective. They also appear to be just as sharp as permanent blades when initially used. When disposable blades are used, the blade is moved along the blade holder over the course of the day. This prolongs the blade's sharpness as different parts of the blade interface the tissue block as the day progresses.

For frozen sectioning, one should try to achieve the thinnest sections possible. Technically it is difficult to get sections thinner than 3 to 4 microns. Sections that are thicker (above 5 to 6 microns) can often be difficult to read as cellular structures do not show very clearly. As mentioned before, thicker sections may be necessary for facilitating good sections of fat, but doing so will compromise evaluation of epidermal aspects. Alternating thicker and thinner sections on a slide is one way to get the best of all worlds.

In the process of cutting, when using a manual system, there are those that feel that a rapid turn of the cutting wheel followed by capture of the specimen on an anti-roll bar or on a chilled camel hair brush is optimal. Others work with a slow, deliberate turn of the hand. In this case, a steady hand is required so that the effect of chatter, ratcheting, or thick-thinning is avoided. The anti-roll bar is a piece of glass that is at the same temperature as the cryostat. When used, it allows a section to slide under as the blade cuts through the block. The use of the bar is a matter of personal preference, and skilled technicians generally feel the anti-roll bar slows them down.

Some histotechnicians have a microscope near the cryostat so they may evaluate unstained sections. With the substage condenser set to a low position to increase contrast, this setup allows the histotechnician to evaluate section quality before staining. This can minimize the need for deeper cuts after the mounting disc is removed from the microtome.

Staining

The most popular stains used in Mohs surgery are hematoxylin and eosin (H&E) and toluidine blue. Maintaining quality on H&E stains can be difficult, and they are subject to pH changes with narrow tolerance ranges over time. Toluidine blue staining is more forgiving, but slightly more time is involved in setting up and, in our experience, must account for variations in local water supply conditions. A well-executed toluidine blue stain is rewarding in that metachromasia of mast cells serves as a built-in positive control. Mucin, when present, stains bright red and attracts the eye to potential tumors. Basal cell carcinomas stain an intense blue (Fig. 2.4) while squamous cell carcinomas will exhibit the greenish hue of prekeratin very clearly in many cases (Fig. 2.5).

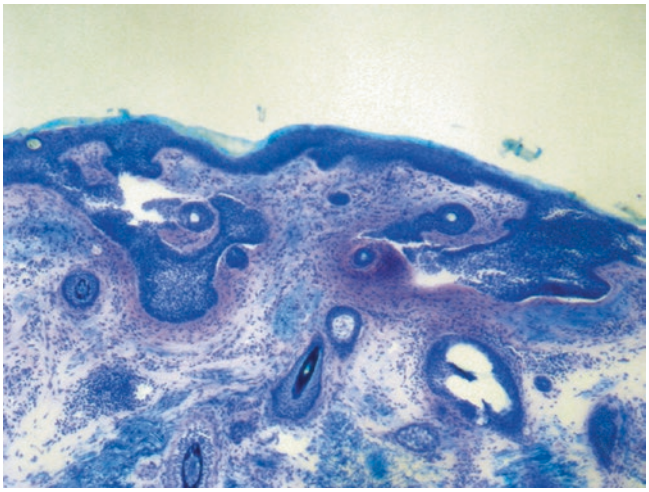

Fig. 2.4 Mucin in the reactive stroma stains a characteristic red and helps in localizing basaloid aggregates of tumor

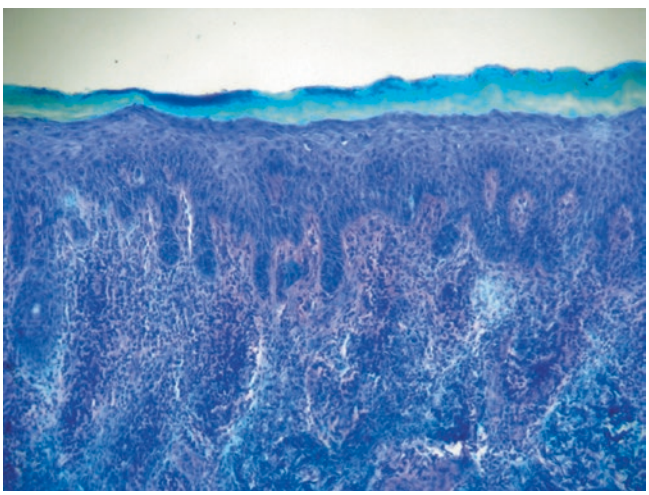

Fig. 2.5 Mucin surrounds large cells with obvious nuclear atypia

Staining is typically done on slides with a sequence that involves the cutting of tissue and the fixation of the tissue in absolute alcohol. This is followed by the removal of excess embedding media and the application and dilution of various stains. Dehydration steps are accomplished with increasing concentrations of alcohol while the clearing of the specimens is classically done with xylene.

Because of xylene's toxic and flammable properties, many xylene substitutes are available. We find that the Limonene xylene replacement is a good substitute that does not affect slide quality and eliminates the risk of carcinogens. Despite this, our histotechnicians still work under a filtered hood to minimize the risk of excess inhalation of any of these volatile substances.

Automatic linear stainers can be time savers and allow the staining process to move smoothly in a busy practice. One concern is that autostainers can be subject to maintenance issues and breakdown. The choice of manual or automatic stainers should be a function of volume and the needs of a particular laboratory.

Trouble Shooting / Quality Assurance

Suboptimal sections arise for myriad reasons. Maintaining communication and feedback between the surgeon and the histotechnician is integral in obtaining optimal slides for evaluation. With a multiheaded microscope, histotechnicians are able to directly correlate their techniques with what the surgeon sees and interprets (Fig. 2.6). For example, missing epidermis on sections can be brought to the attention of the histotechnician and identified. Then by changing the axes of the block holder, specific areas of the tissue block can be focused on for deeper sectioning.

The quality assurance process must occur as needed on a case by case basis and with regulatory bodies as part of a scheduled process by which slides are pulled and reviewed. Meticulous logs should be kept and reviewed with regard to changing of stains and reagents, crytostat maintenance and microscope calibration (See Table 2.1).

The following issues are commonly encountered and can be easily addressed:

Tears can result from the histotechnician flattening the specimen aggressively, or from the surgeon cutting inapparent notches. This problem often arises when the surgeon obliquely cross-cuts the base of the specimen while obtaining the Mohs layer. Tears can compromise visualization of the entire margin, and a concerted effort should be made to avoid them.

Chatter, or the "vertical blinds" effect, is likely a result of inadequate tightening and lubrication of the microtome gears. The resulting uneven motion and force can lead to

Fig. 2.6 The authors examining Mohs sections at the multiheaded microscope

separation in a linear fashion, tears or frank tissue dropout.

Holes in tissue sections are generally unacceptable. While a hole may represent a space occupied by a cyst or milia, it may represent an island of tumor that is retracted from surrounding stroma. Holes should not be considered acceptable unless the surgeon inspects both the specimen and the block and determines that a hole is indeed a result of a tear induced by the flattening and mounting of the specimen. If the specimen appears to be intact, deeper specimens should be obtained until the hole has disappeared.

Hair, especially when large, can result in pulling or fracture of tissue that can affect the epithelial margin. Coarse hairs can also quickly dull the cutting blade. If working in extremely hairy areas, clipping of the hair prior to the surgery could ameliorate this effect. Hairs can also be plucked from the specimen prior to embedding; in-vivo plucking is even better, if feasible.

Air bubbles are best prevented with proper coverslipping. This involves applying media to the glass slide and slowly lowering the coverslip, like a hinged door, onto the media. Doing this too quickly can trap bubbles and not allow the bubbles to be naturally forced out. If air bubbles are noted after the fact and while the media is still viscous, a blunt probe or cotton-tipped applicator can be used on the coverslip to gently force the bubble to the nearest edge. If necessary, dried slides can be be "recleared" at a later time and re-coverslipped if needed. Slides can be restained by decolorizing through reversing the staining process and restaining with a different stain. If this is done, documentation of one's rationale should be charted for medicolegal reasons.

Table 2.1 Maintenance record – crytostat

Month _____ Year _____

Activity	Clean interior	Thermometer check	Moving components	Clean air filter	Preventative maintenance	Defrost machine	Problems supervisor attention
1							
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Part II

Tumors of the Epidermis/Adnexae

Histology with Regional and Ethnic Variation

3

Michael B. Morgan and John R. Hamill Jr.

The human skin comprises a complex trilaminar consisting of the superficial epithelium, mid-dermis with adnexae and deeper subcutaneous fat. The histological features of skin and the adnexae are diverse and confounded by limitations imposed by frozen section technique, racial/gender variation and degenerative conditions ascribed to the aging process and exposure to ultraviolet light. This chapter will provide a comprehensive review of the histological features of the epithelium dermis and subcutaneous fat with associated adnexae seen on the skin and mucous membranes. It will include individual variations due to racial or gender difference as well as degenerative alterations as seen in the aged or sun-damaged patient.

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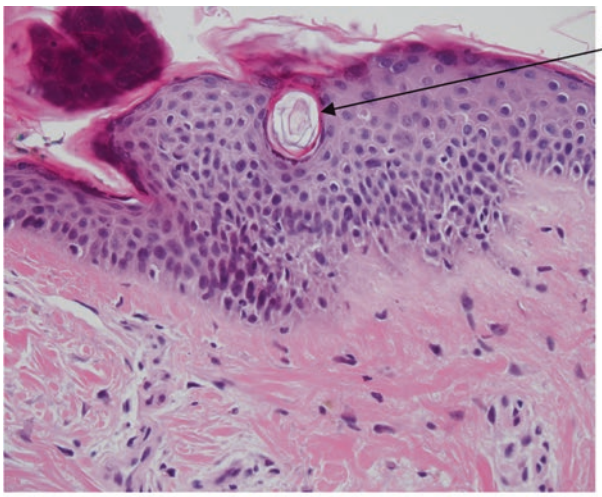
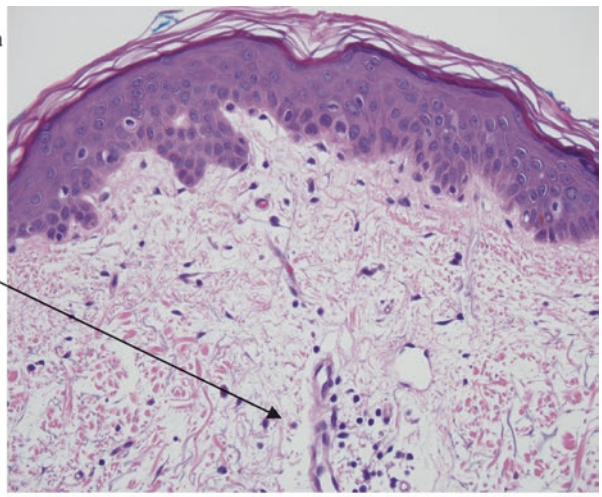
The Epithelium
Normal Adult Histology & Regional Variation



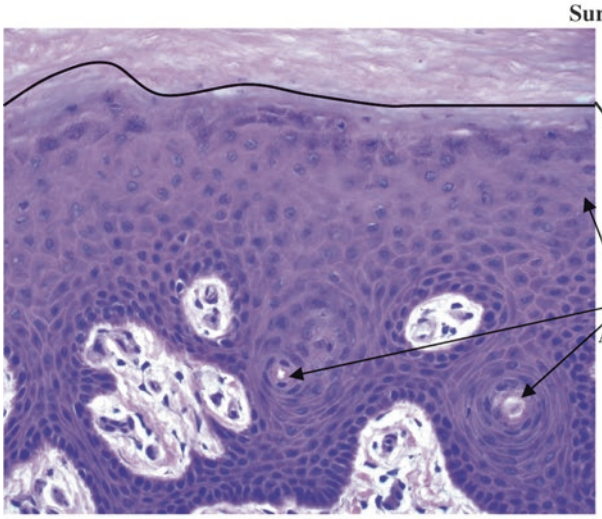
FACE *HIGH* 3-1

- Basket-weave Orthokeratin
- Increased Acrotrichia



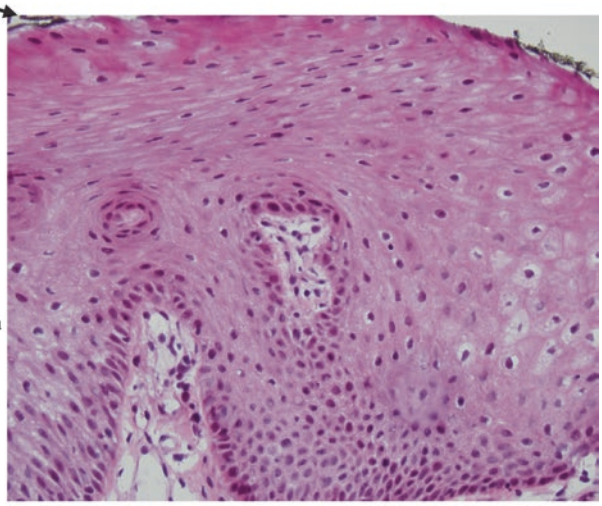
TRUNK *HIGH* 3-2

- Mild Solar Elastras (dermatoheliosis)
- Less Conspicuous Follicles
- Capillary ectasia (dermatoheliosis)



ACRAL *HIGH* 3-3

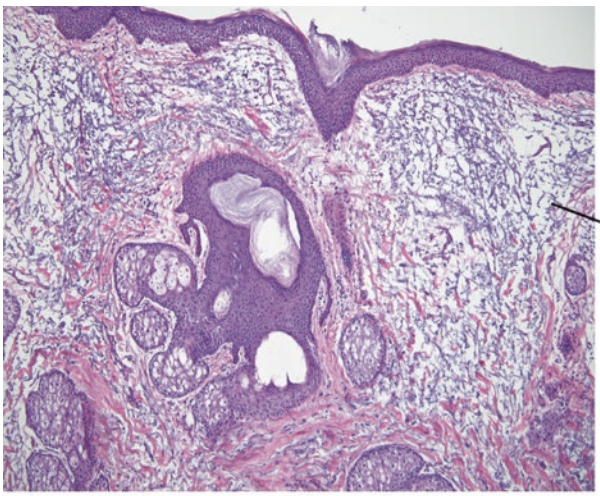
- Increased Acrosyringia
- Lamina Lucida
- Compact Orthokeratin



MUCOSA *HIGH* 3-4

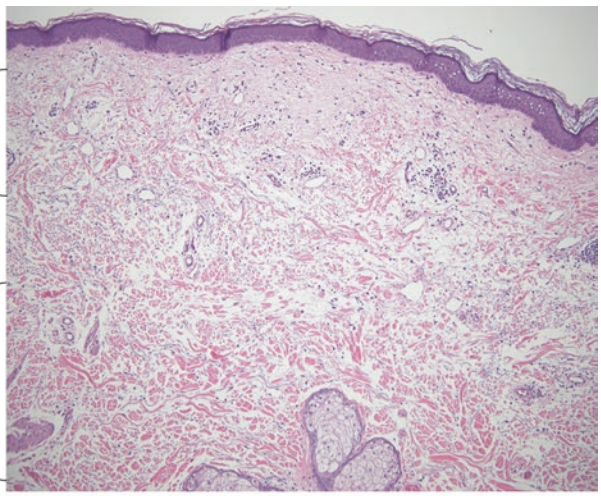
- No Stratum Corneum
- Parakeratotic Surface
- No Adnexae

Dermis
Normal Adult Histology & Regional Variation



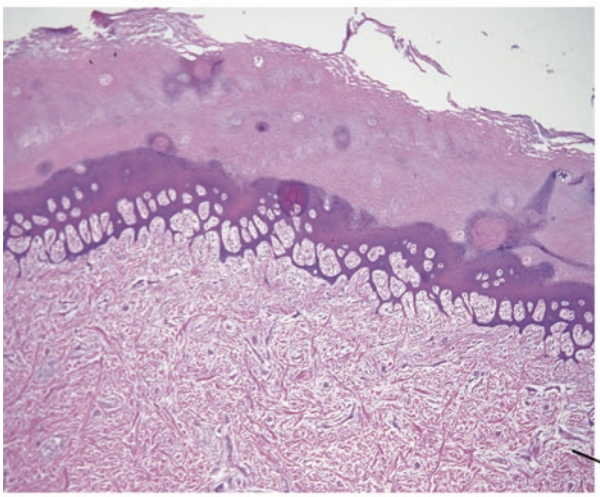
FACE *MEDIUM* 3-5

- Conspicuous Follicles with Lymphocytic Infiltrate
- Solar Elastosis – Capillary Ectasia



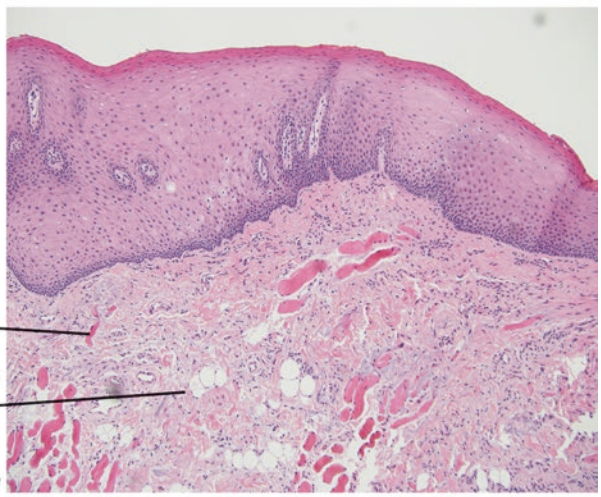
TRUNK *MEDIUM* 3-6

- Conspicuous zonation between Papillary/Reticular Dermis



ACRAL *LOW* 3-7

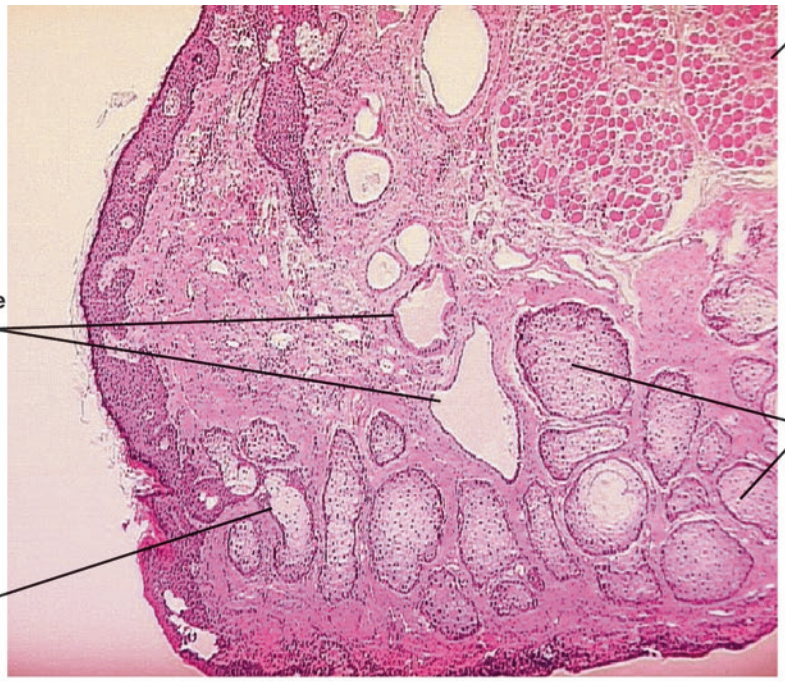
- Conspicuous Eccrine Ducts
- Compact Dermal Collagen



MUCOSA *MEDIUM* 3-8

- No Adnexae
- Superficial Adipose Tissue
- Skeletal muscle in close proximity to the mucosa

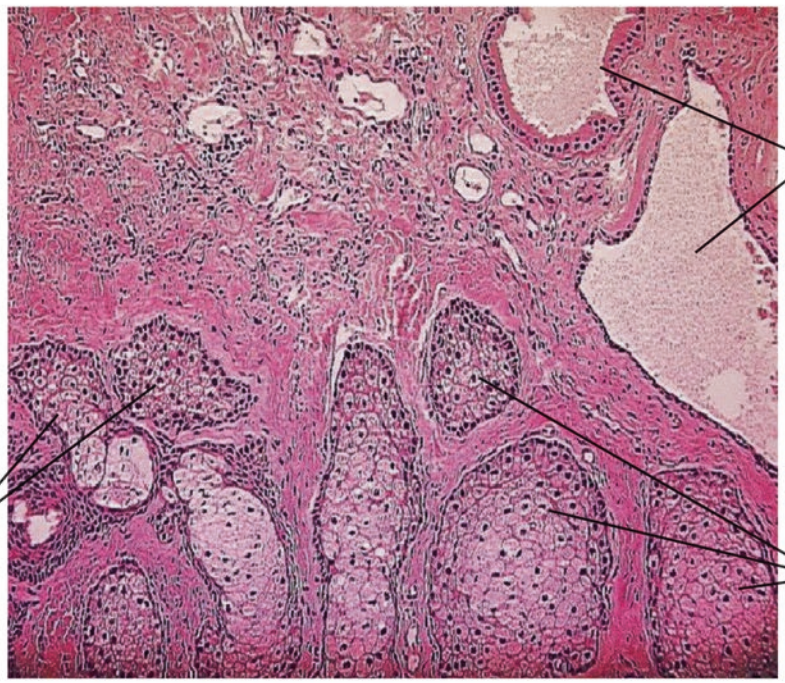
Normal Eyelid Anatomy



- Lobed structure with epithelium circumferentially surrounding specimen

Note: Bundles of skeletal muscle and sebaceous lobules

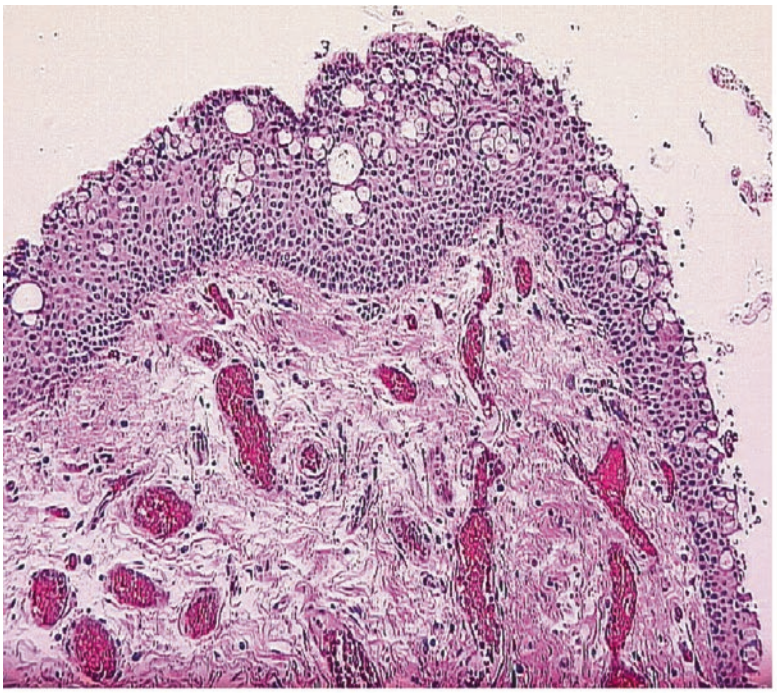
3-9



- Detail of Zeis and Meibomian glands

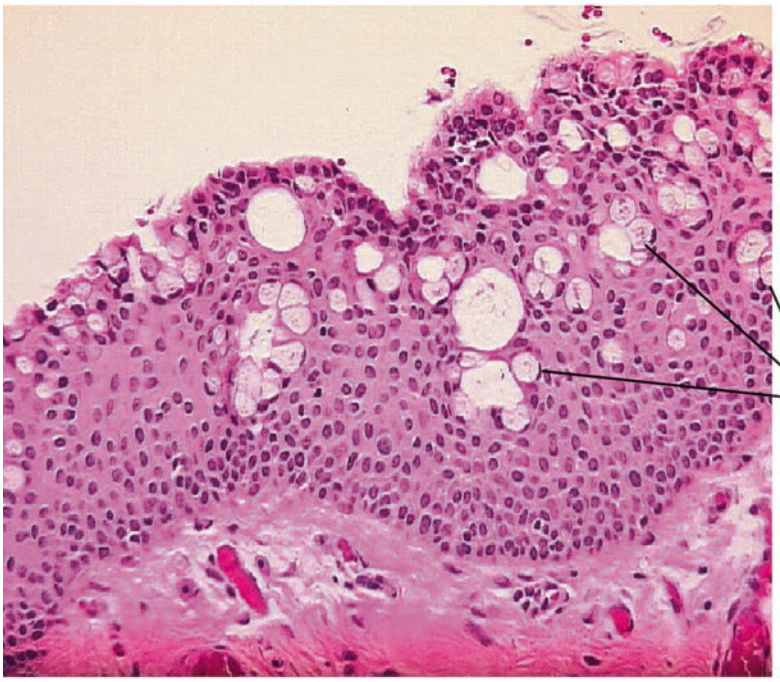
3-10

Conjunctiva



MEDIUM 3-11

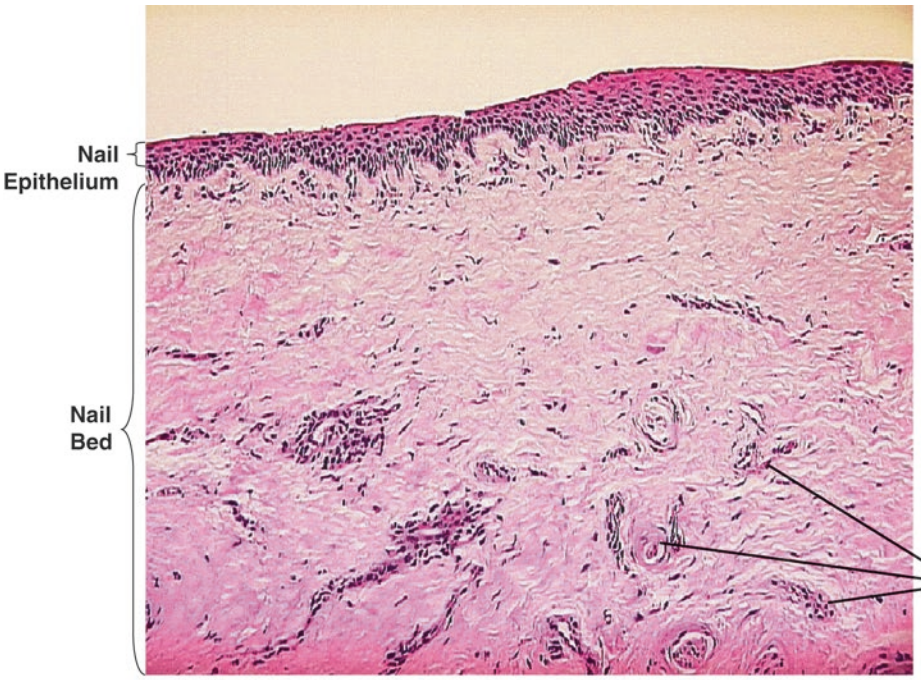
- Non-keratinizing epithelium with abundant mucous (goblet) cells
- Loose submucosa with increased number of capillaries



HIGH 3-12

- High power detail showing mucous (goblet) cells

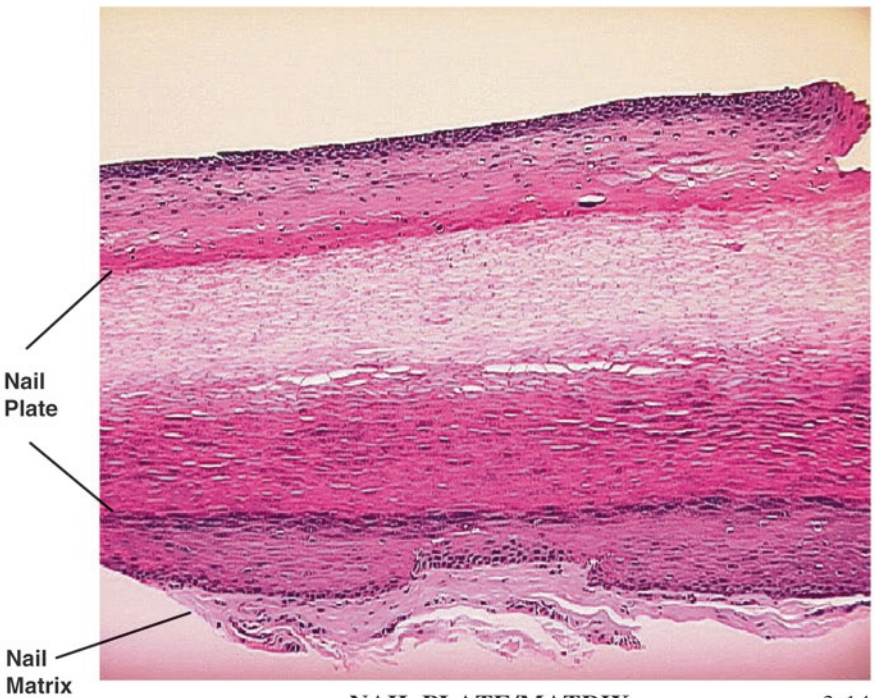
Nail Anatomy



Note: Non-keratinizing epithelium with corrugated (thin rete) appearance

Note: Bed with increased blood vessels

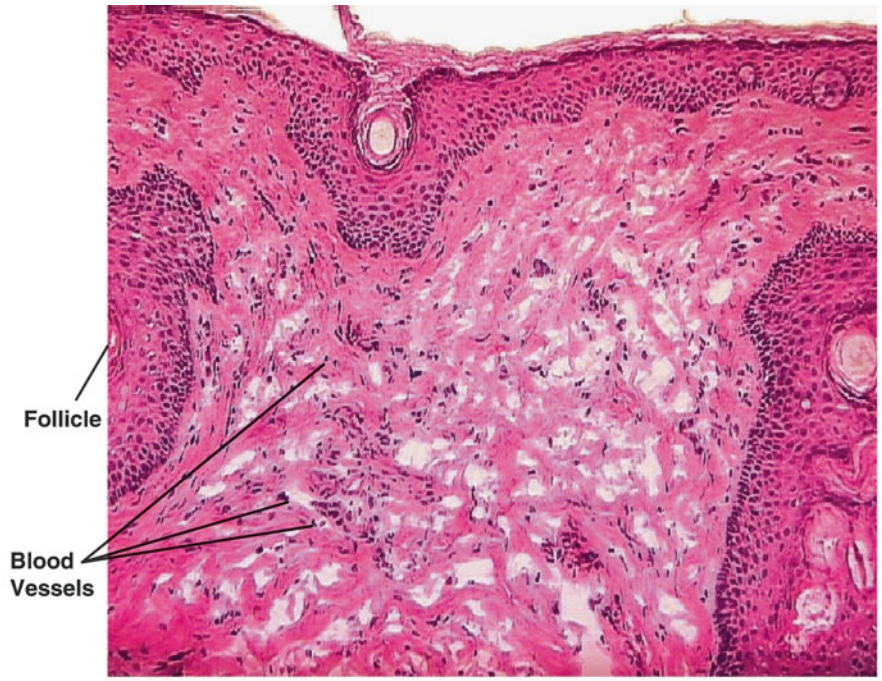
NAIL BED 3-13



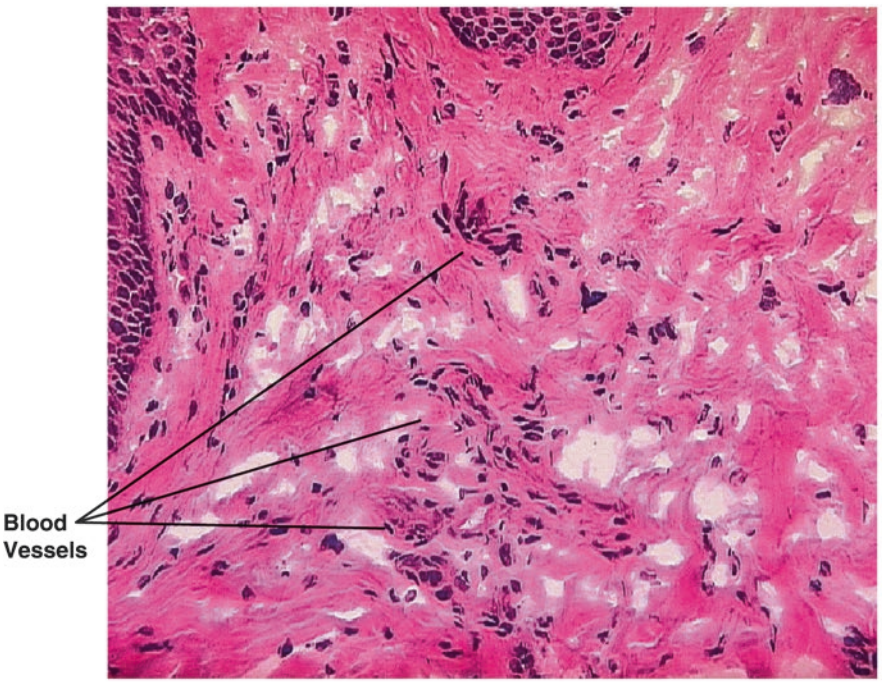
Note: Trilaminar appearance of nail plate

NAIL PLATE/MATRIX 3-14

Nasal Mucosa



LOW 3-15

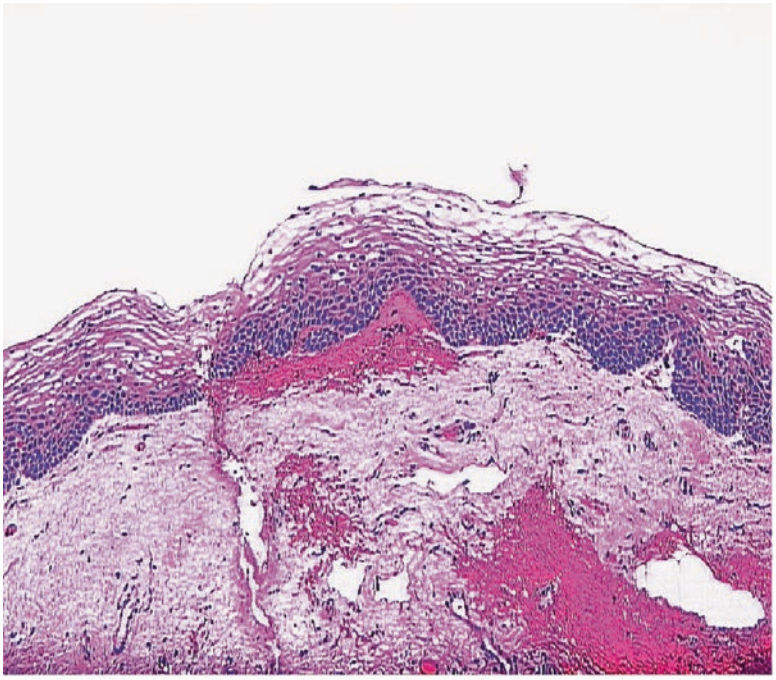


HIGH 3-16

- Nasal mucosa with increased vellus/terminal follicles

Note: Absence of solar elastosis with increased blood vessels

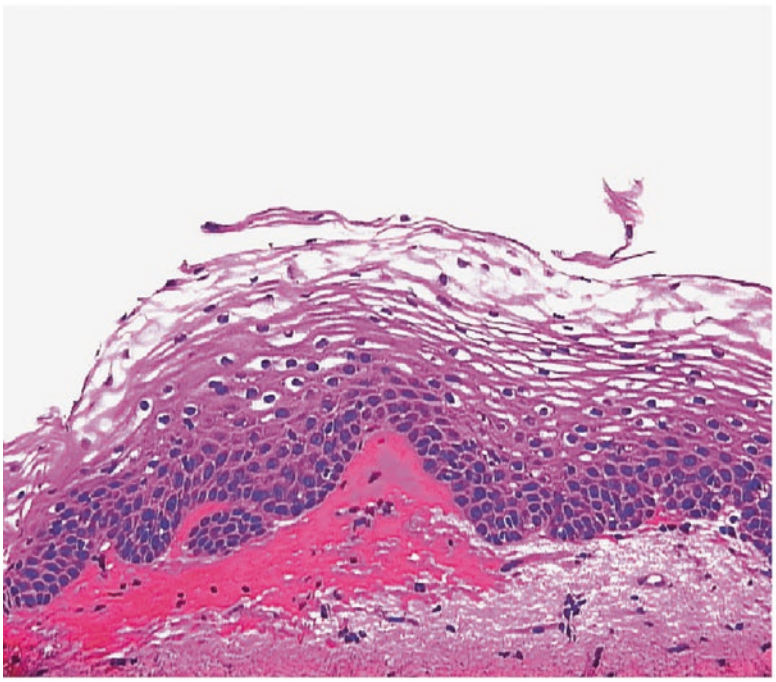
Anal Mucosa



MEDIUM 3-17

- Non-keratinizing squamous epithelium

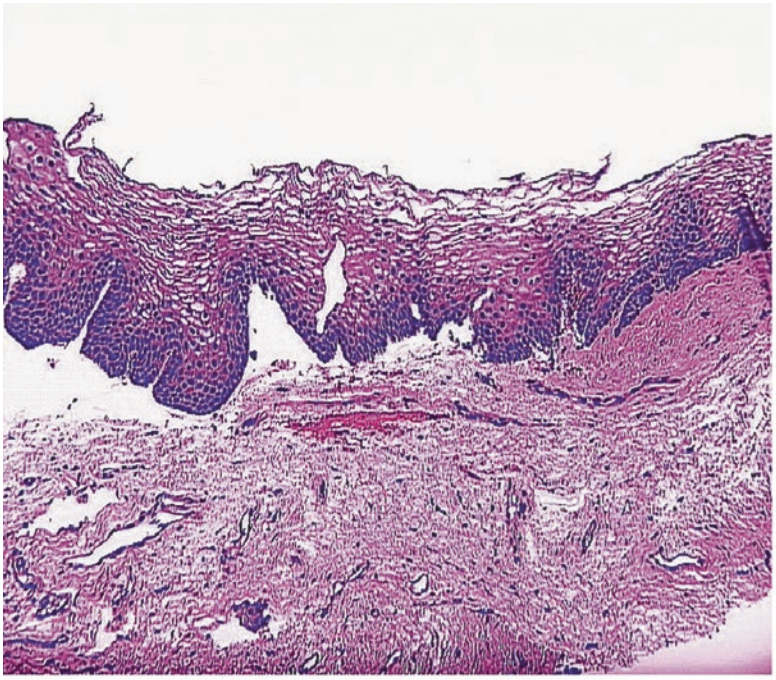
Note: Vascularized submucosa



HIGH 3-18

- Detail of epithelium

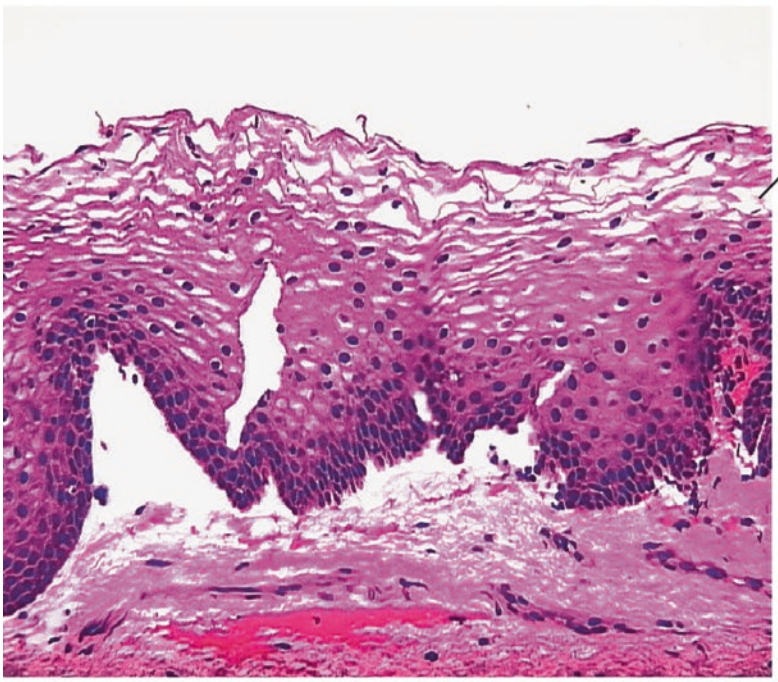
Vagina Mucosa



MEDIUM 3-19

- Non-keratinizing epithelium

Note: Fibrous appearing submucosa

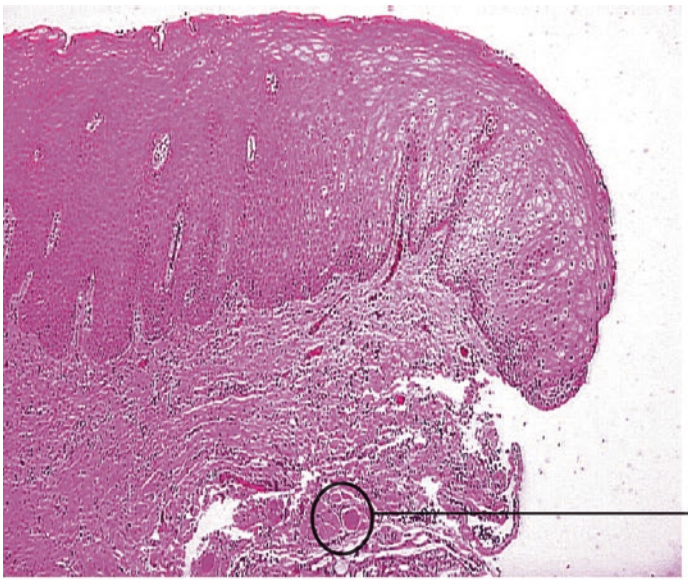


HIGH 3-20

- Detail of epithelium

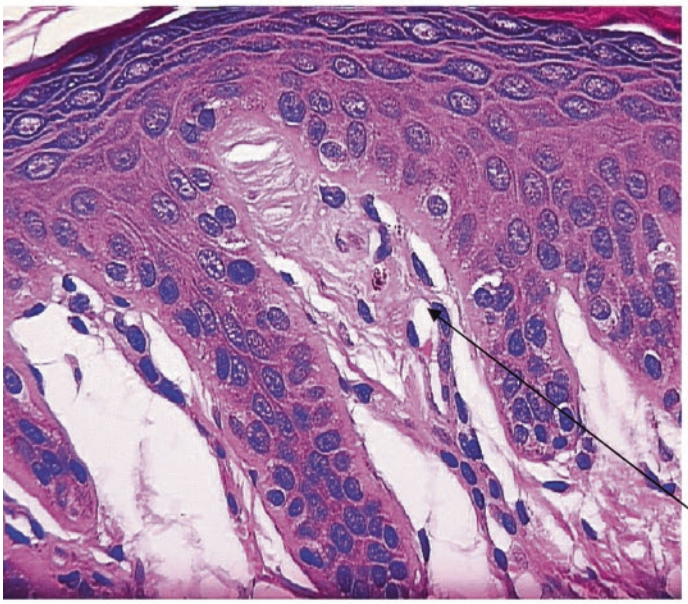
Note: Glycogenation (clearing) of the superficial keratinocyte cytoplasm

Lip Mucosa



MEDIUM 3-21

- Lip mucosa
- Proximity of skeletal muscle to mucosa without interposed subcutaneous fat

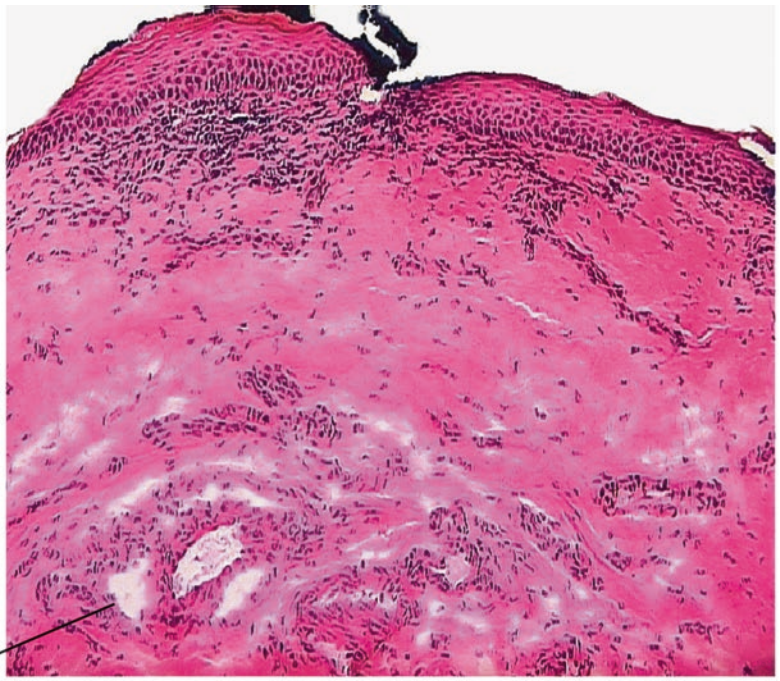


HIGH 3-22

- Detail of specialized touch receptor found on lips and other mucosal sites.

Note: Keratinized stratum corneum with hypergranulosis as seen with chronic mucosal irritation (leukokeratosis)

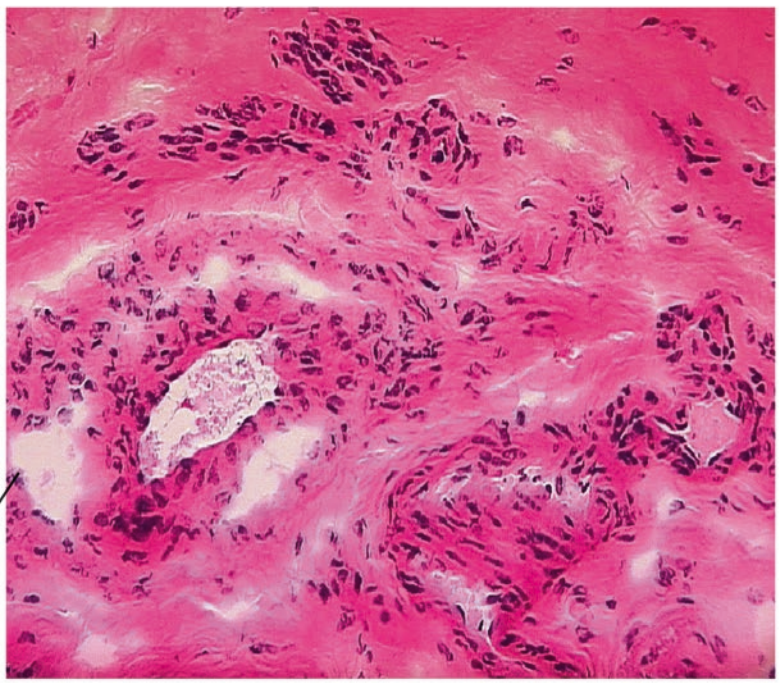
Penile Mucosa



LOW 3-23

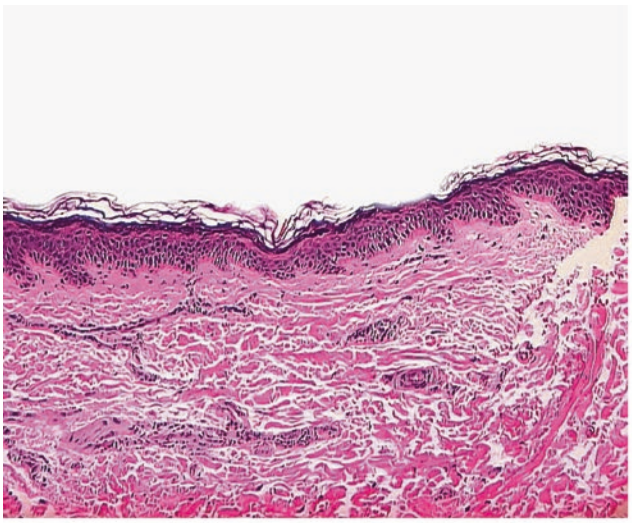
- Penile mucosa with thinned keratinizing epithelium and flattened rete ridges

Note: Prominent blood vessels

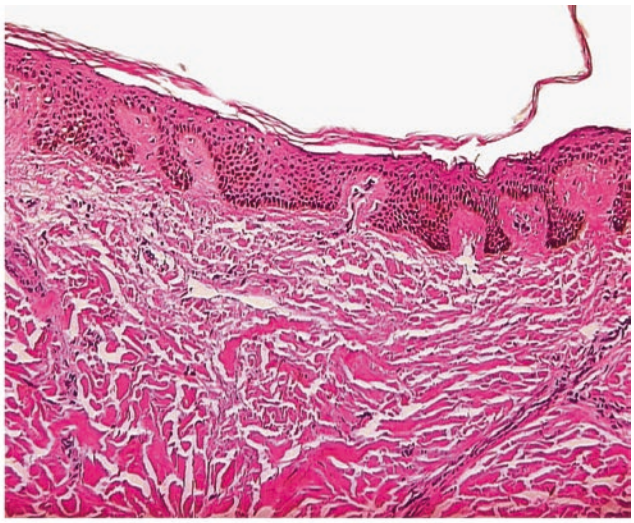


HIGH 3-24

Ethnic Variations

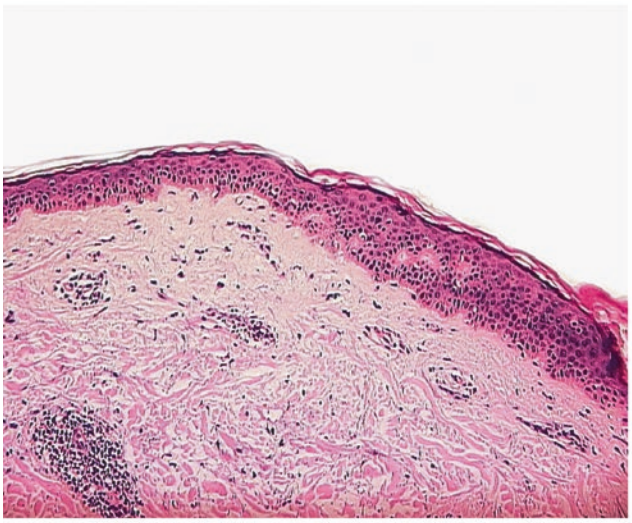


CAUCASIAN SKIN 3-25



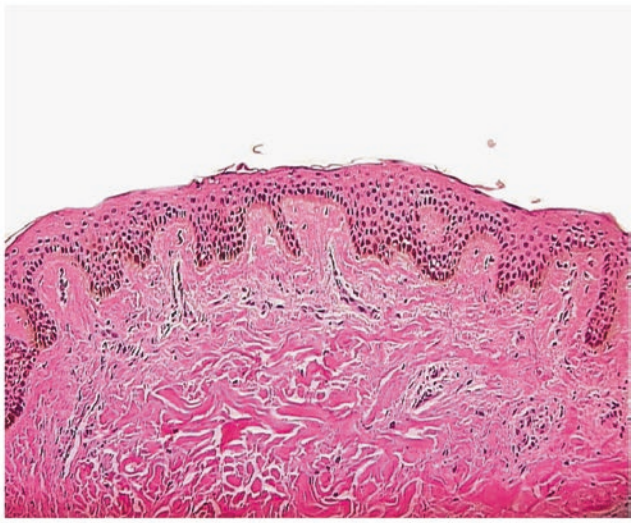
AFRICAN AMERICAN SKIN 3-26

- Pronounced pigmentation, normal number of melanocytes



ASIAN AMERICAN SKIN 3-27

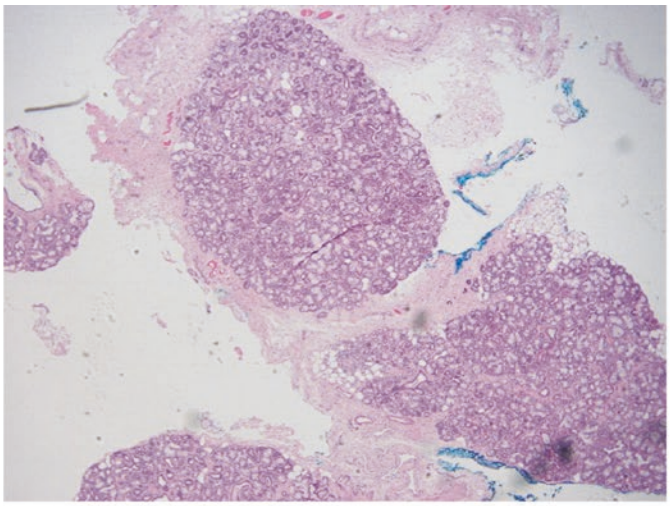
- Slight increase in pigmentation, normal number of melanocytes



HISPANIC SKIN 3-28

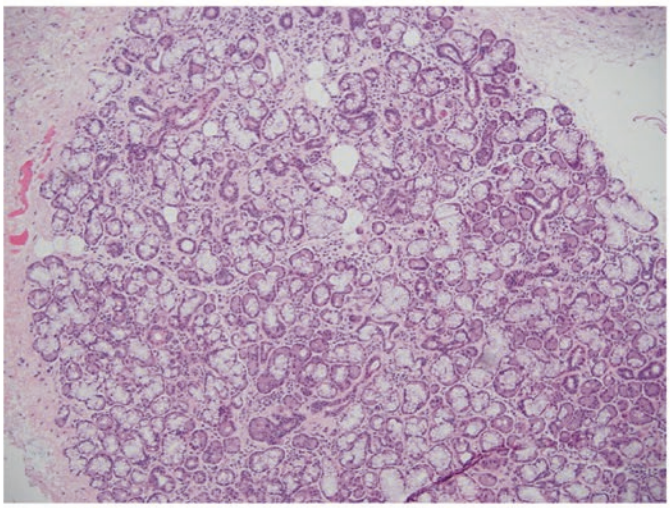
- Modest increase in pigmentation, normal number of melanocytes

Salivary (Minor) Gland



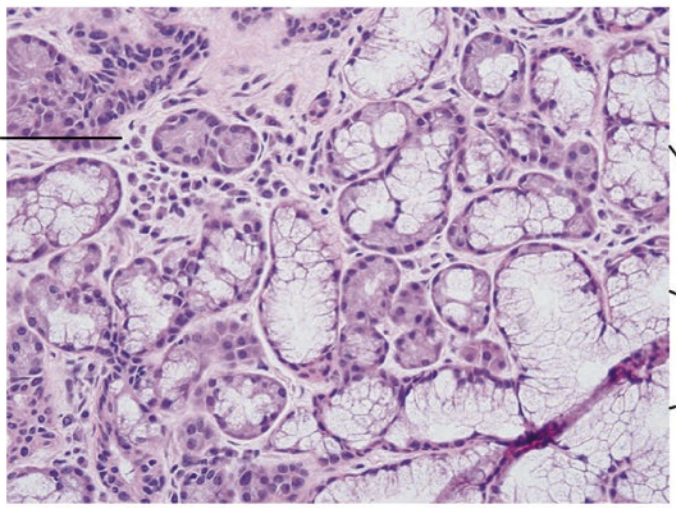
- Rounded glands

LOW 3-29



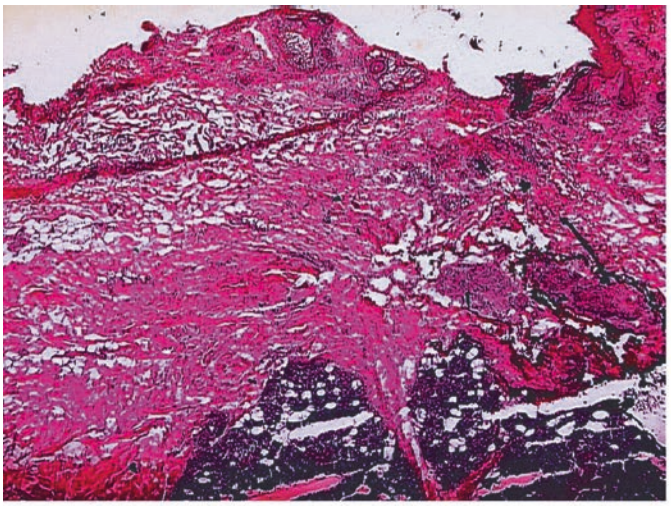
- Well-circumscribed collection of biphasic glands

MEDIUM 3-30



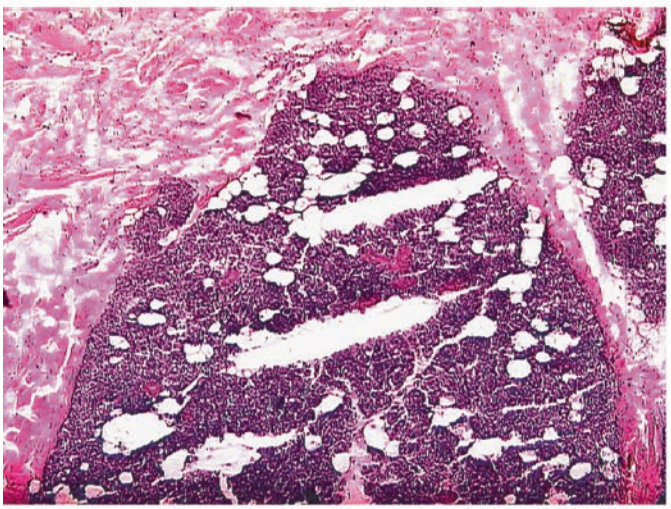
HIGH 3-31

Parotid Gland



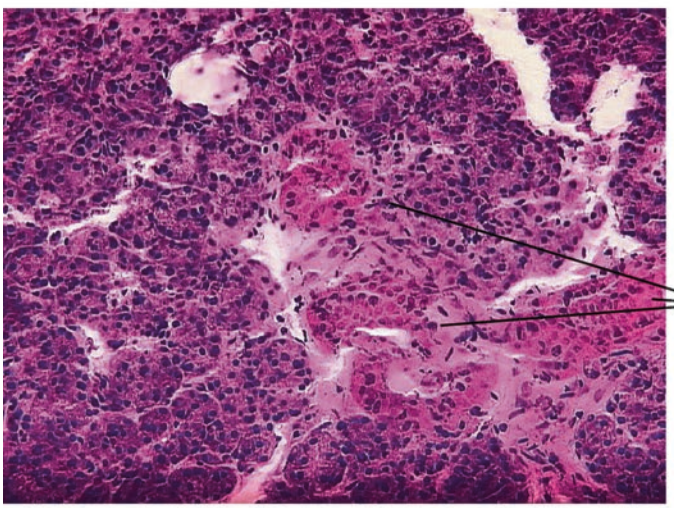
- Low-power depiction of parotid gland juxtaposed to epithelium

LOW 3-32



- Detail of parotid gland showing predominance of purple serous glands (in contrast to minor salivary glands)

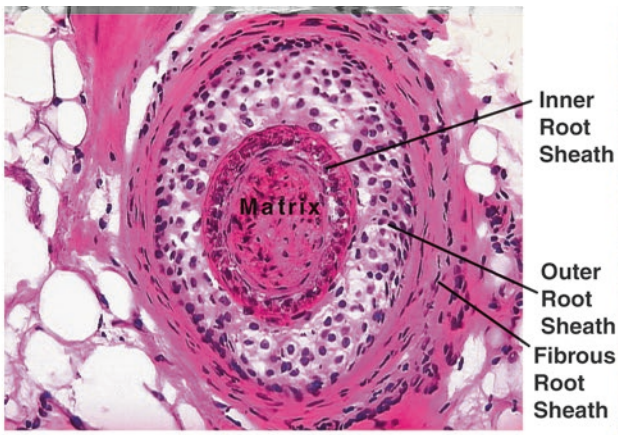
MEDIUM 3-33



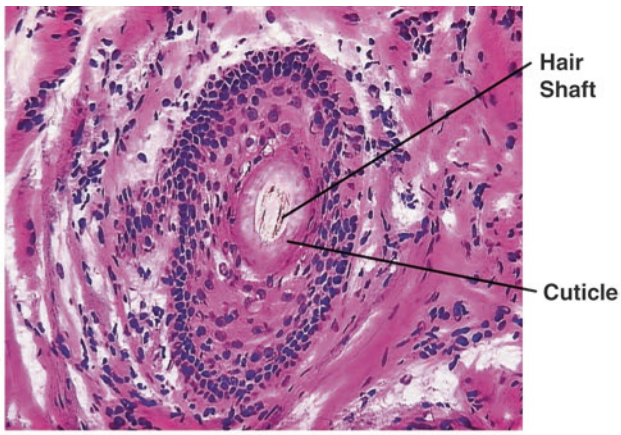
- Interspersed oxyphilic (oncocytic) ducts

HIGH 3-34

Normal Dermal and Subcutaneous Structures
Hair Follicle and Sebaceous Lobule

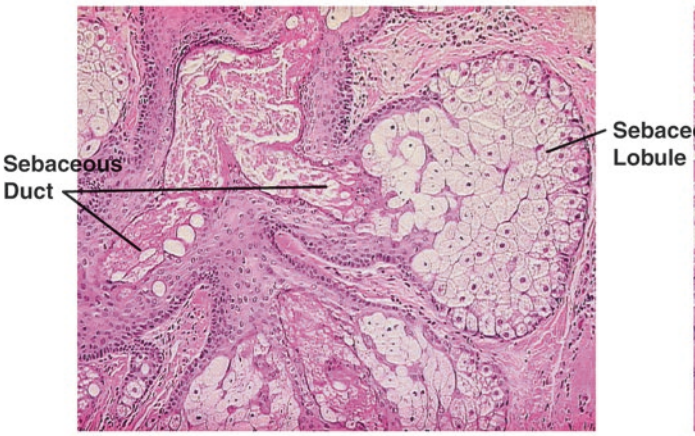


CROSS SECTION AT FOLLICULAR BASE *HIGH* 3-35

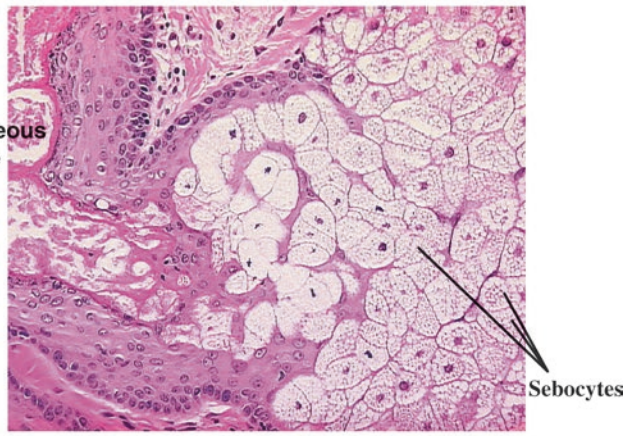


CROSS SECTION AT FOLLICULAR INFUNDIBULUM *HIGH* 3-36

- Central matrix, surrounded by inner root sheath, clear outer root sheath and finally fibrous root sheath

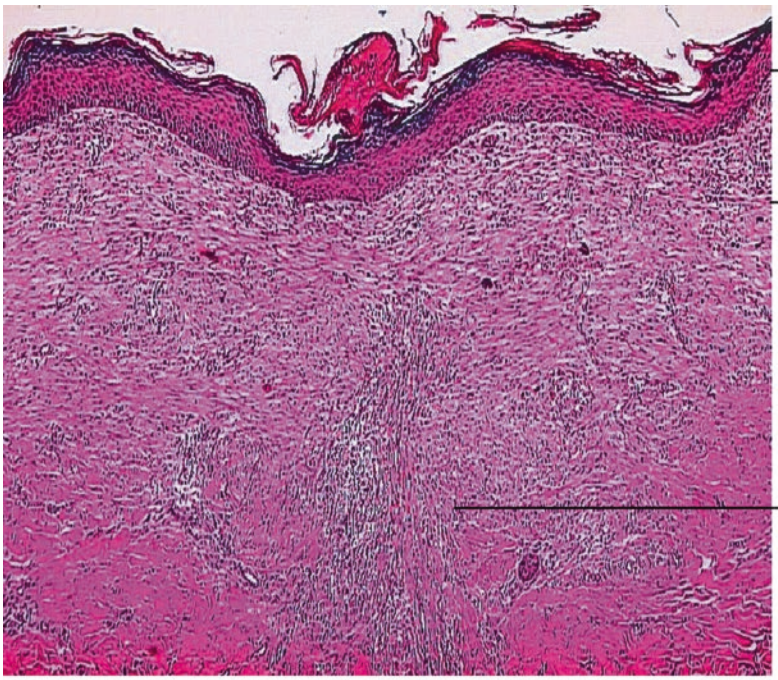


SEBACEOUS LOBULE *MEDIUM* 3-37

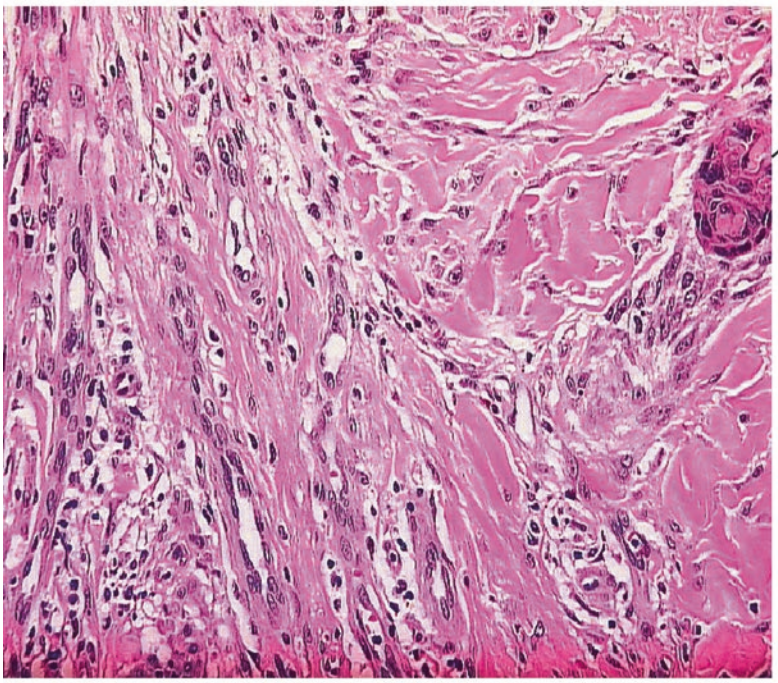


SEBACEOUS LOBULE *HIGH* 3-38

Fresh Scar

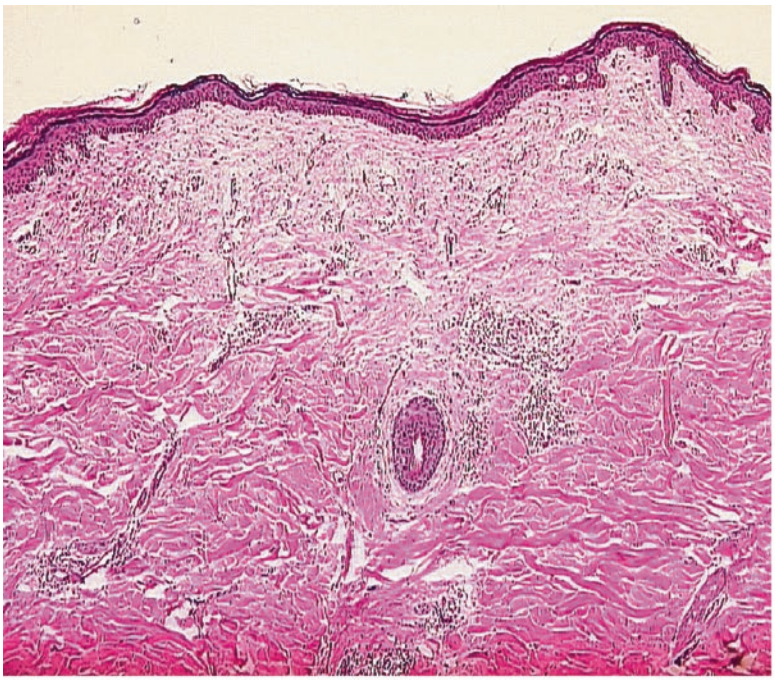


LOW 3-39



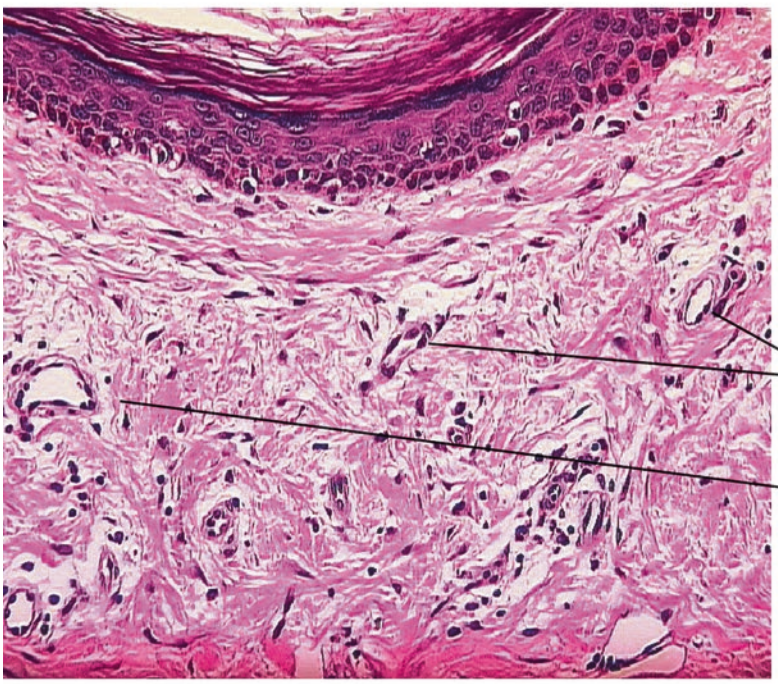
HIGH 3-40

Old Scar



- Old scar site with less cellular dermis

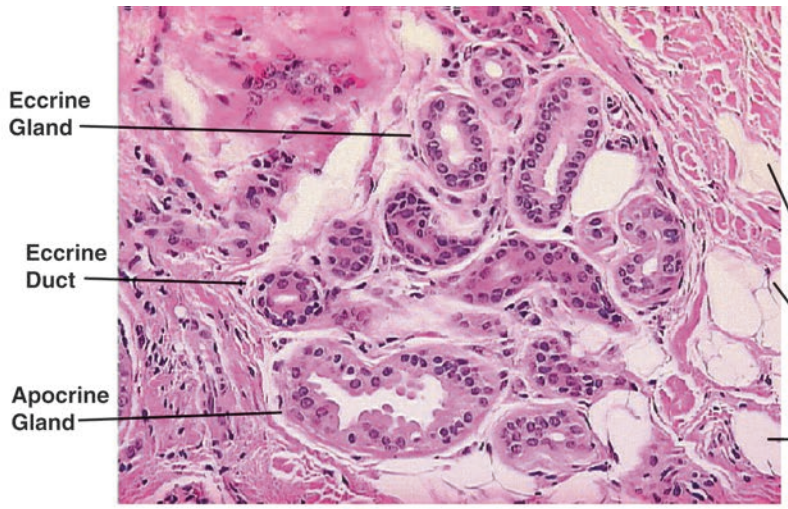
LOW 3-41



- Paucicellular dermis with gaping capillaries

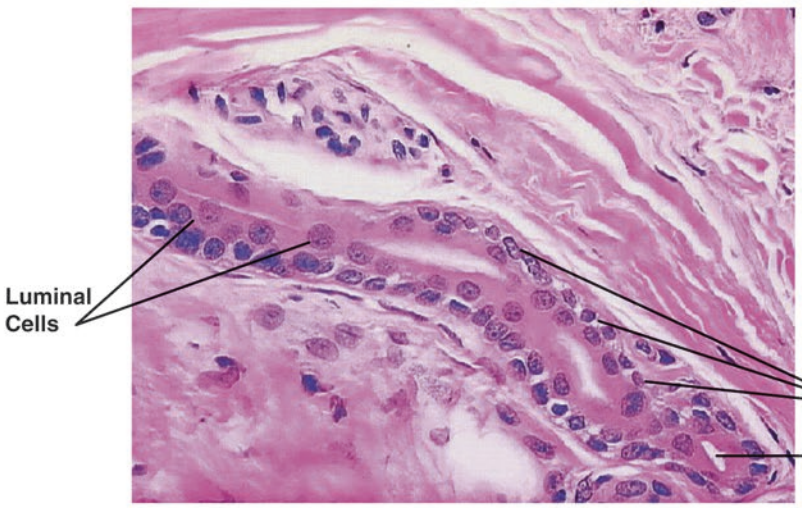
HIGH 3-42

Normal Dermal and Subcutaneous Structures
Apocrine and Eccrine Glands



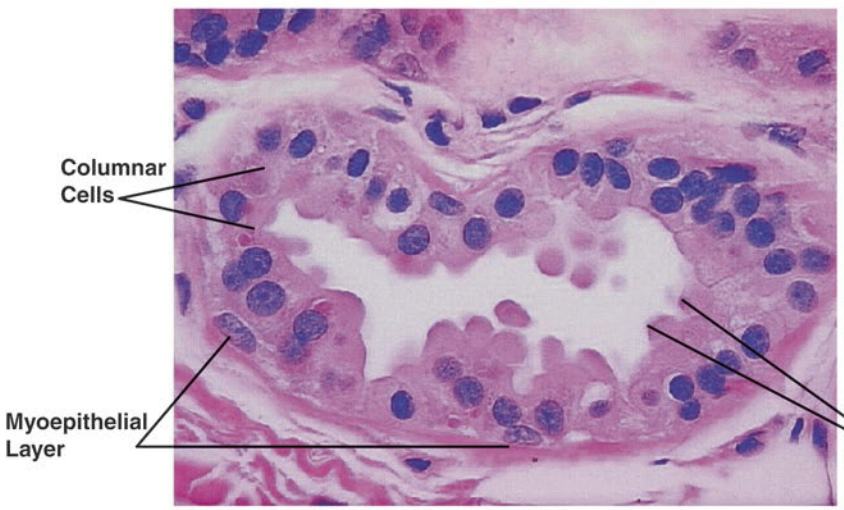
- Bundled appearance of eccrine glands in the deep dermis
- Usually rimmed by adipocytes

LOW 3-43



- Detail of eccrine duct with basilar cuboidal myoepithelial cells and columnar inner layer of luminal cells
- Luminal cells form a common lining border known as the cuticle

MEDIUM 3-44

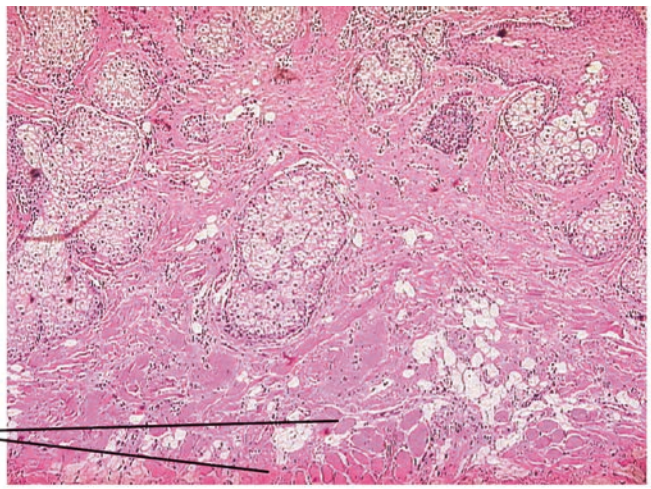


- Detail of apocrine glands composed of outer discontinuous myoepithelial layer and inner stratified columnar cells

Note: Apical snout-like decapitation secretion

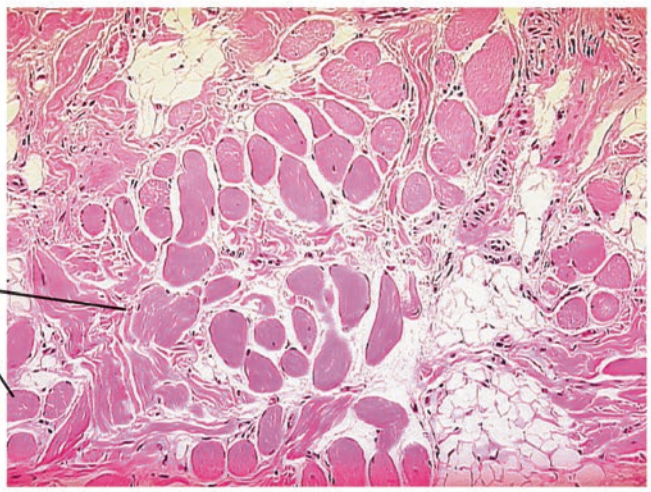
HIGH 3-45

Normal Dermal and Subcutaneous Structures
Skeletal Muscle



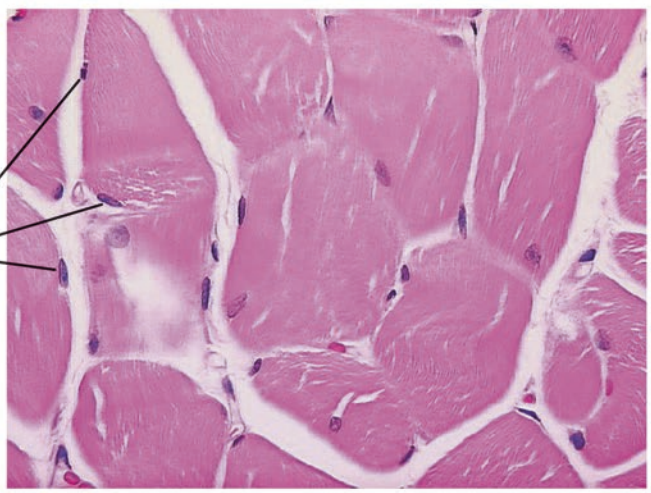
LOW 3-46

- Skeletal muscles seen in close proximity to the dermis (within subcutaneous fat) of the face
- Most commonly seen in periocular or perioral sites



MEDIUM 3-47

- Typical "bundled" appearance of skeletal muscle
- In contrast to collagen bundles, more discrete, round-to-oval and surrounded by nuclei



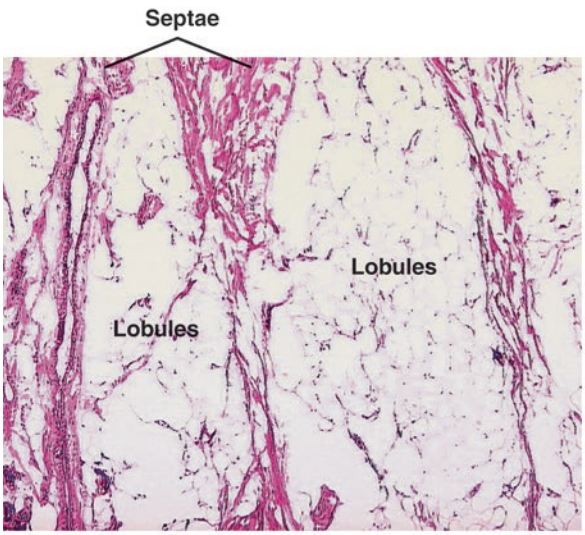
HIGH 3-48

- Detail of skeletal muscle

Note: Nuclei surrounding sarcoplasm

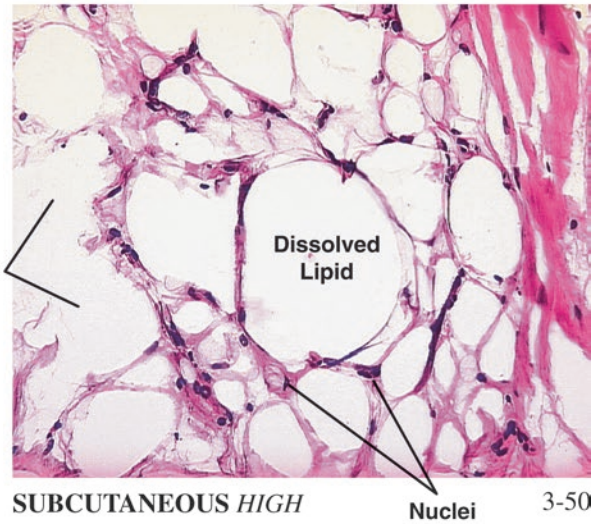
Note: Cytoplasmic striations

Normal Dermal and Subcutaneous Structures
Subcutaneous Fat/Cartilage



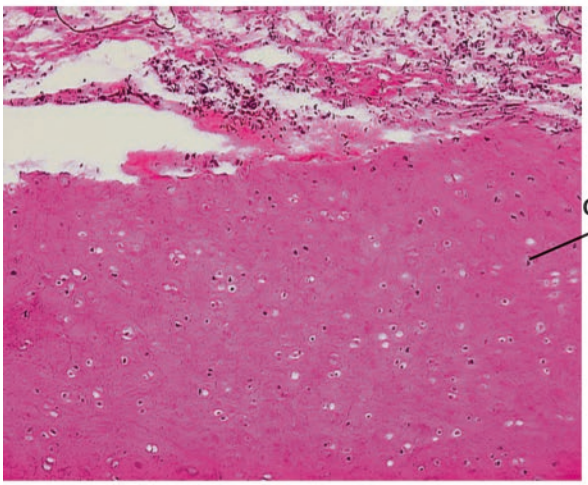
SUBCUTANEOUS *LOW* 3-49

- Subcutaneous fat composed of fibrous septae and adipocytes.
- Typical frayed appearance of fat with frozen sections



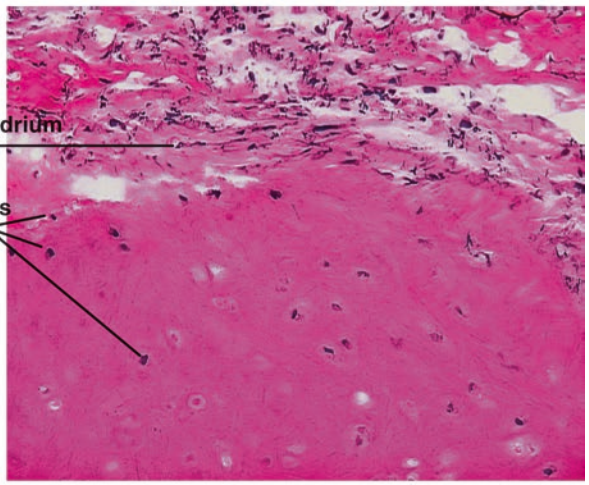
SUBCUTANEOUS *HIGH* 3-50

- Compressed nuclei forming signet ring-like morphology. Normal to see adipocyte heterogeneity



CARTILAGE *LOW* 3-51

- Lacunae consisting of chondrocytes embedded in pink chondroid matrix

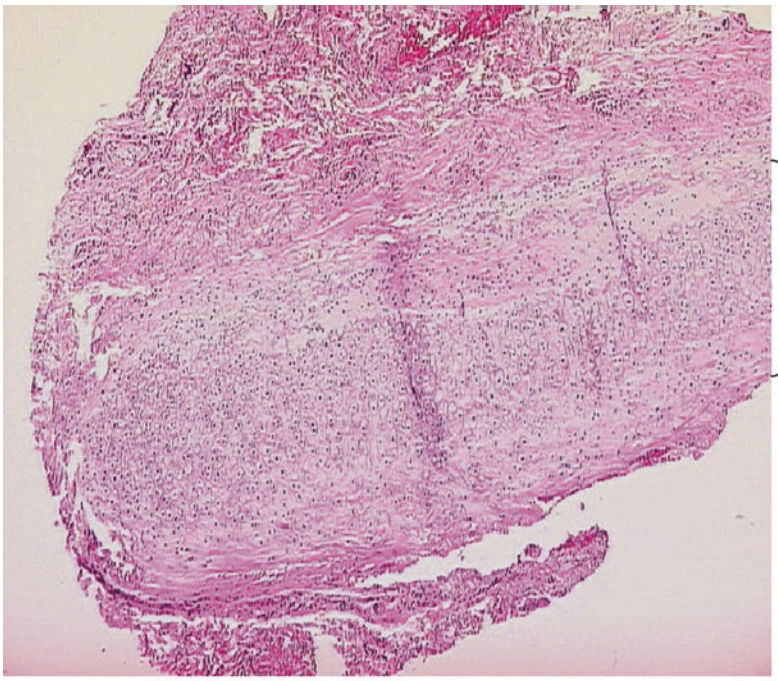


CARTILAGE *HIGH* 3-52

- Chondrocyte nuclei within lacunae

Note: The presence of a fibrous perichondrium

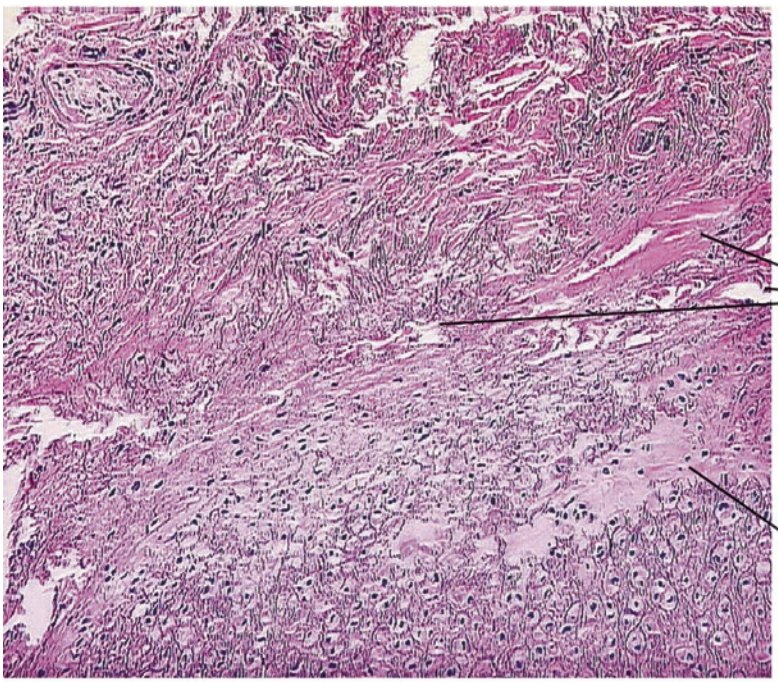
Cartilage



- Nodular aggregate of curretted cartilage sample

Cartilage

MEDIUM 3-53



- Detail of cartilage showing purple staining chondrocytes with focal myxoid pooling

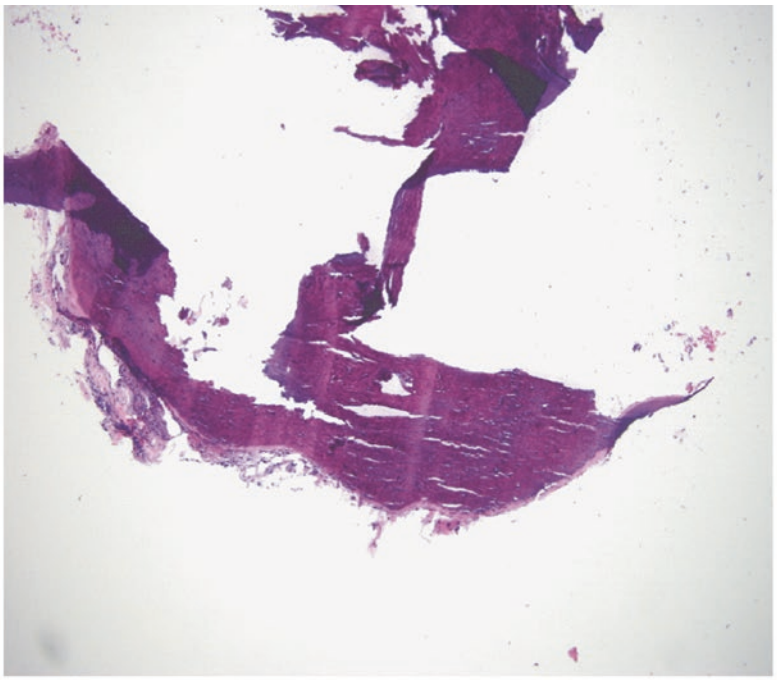
Perichondrium

Myxoid Pooling

Chondrocytes

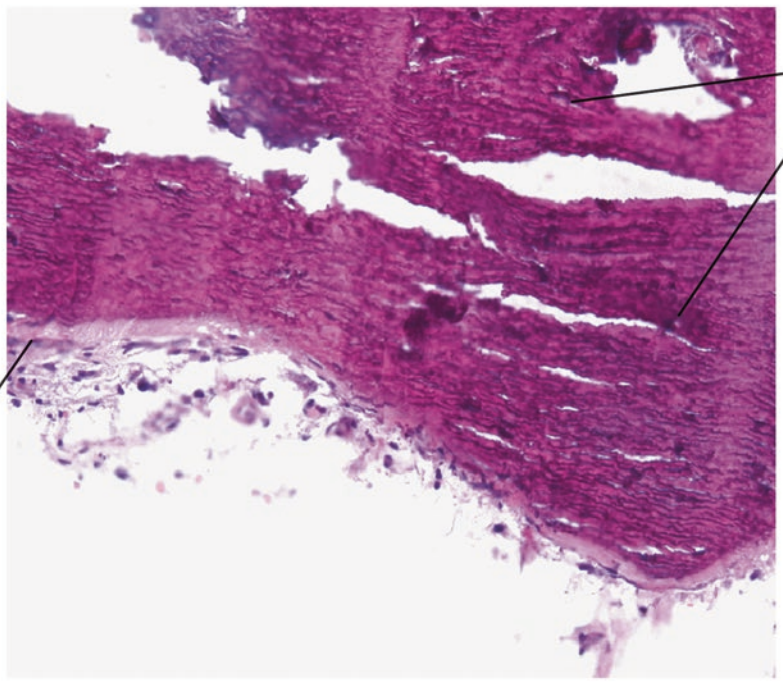
HIGH 3-54

Bone/Periosteum



- Jagged purple fragment
- Fragmented due to density and cutting artifact usually submitted as small pieces

MEDIUM 3-55

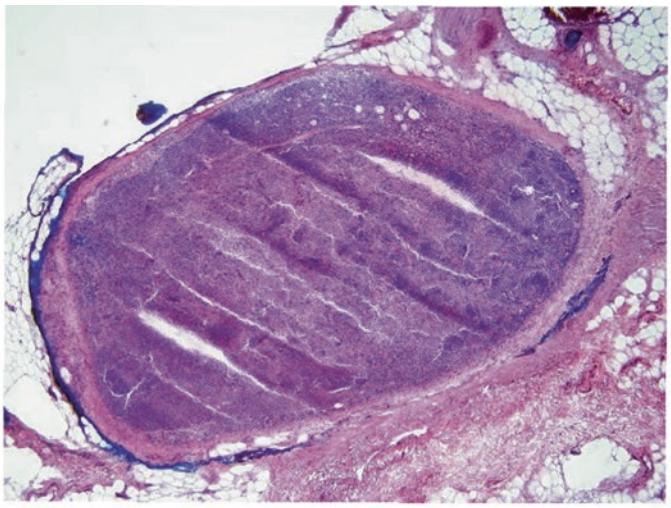


- Laminated pink/purple bone

Note: Thin light pink periosteum
Note: Scattered osteocytes

HIGH 3-56

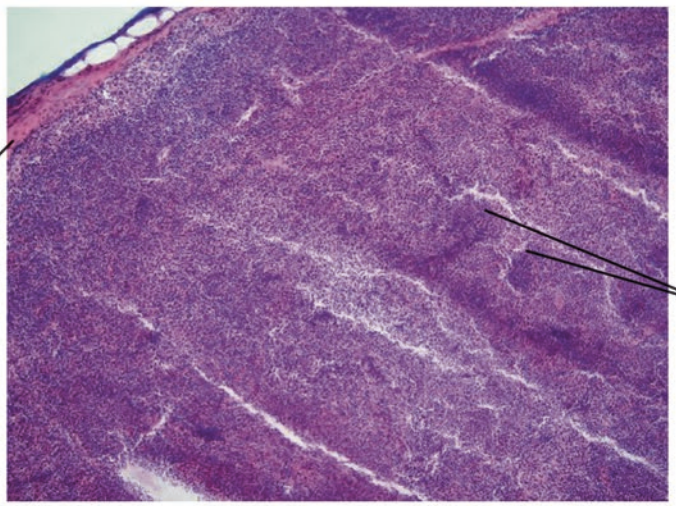
Lymph Node



LOW 3-57

- Low-power photomicrograph of lymph node

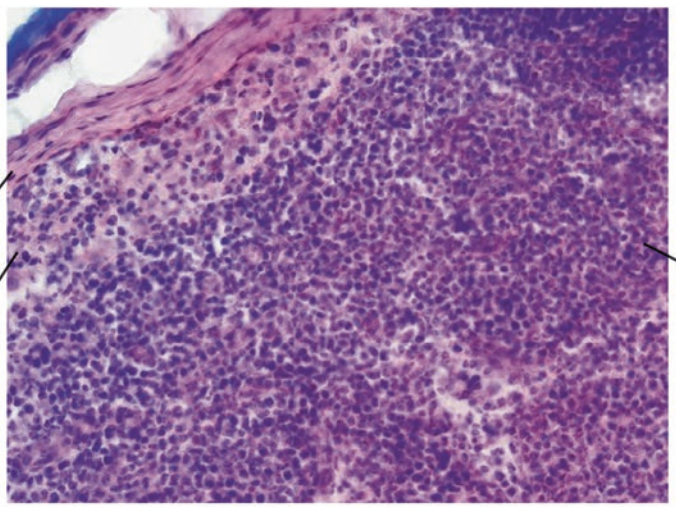
Note: Location within subcutaneous fat



MEDIUM 3-58

- Detail of lymph node

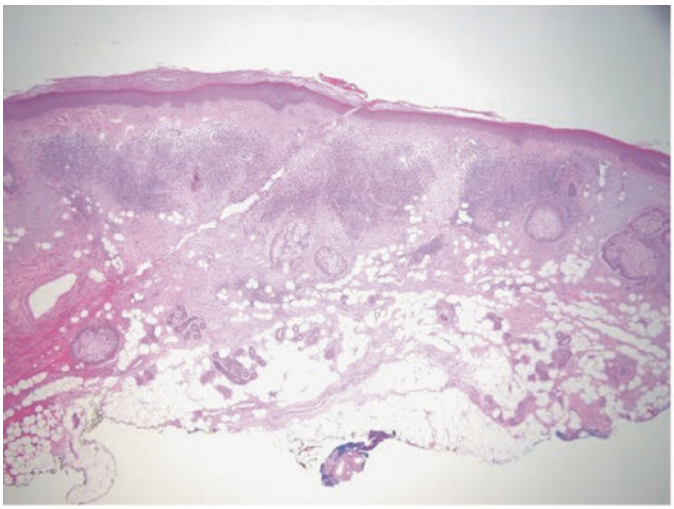
Note: Capsule of lymph node and alternating dark (follicular) and lighter (interfollicular) zones



HIGH 3-59

- Detail of capsule, subcapsule sinus and follicle lymph node

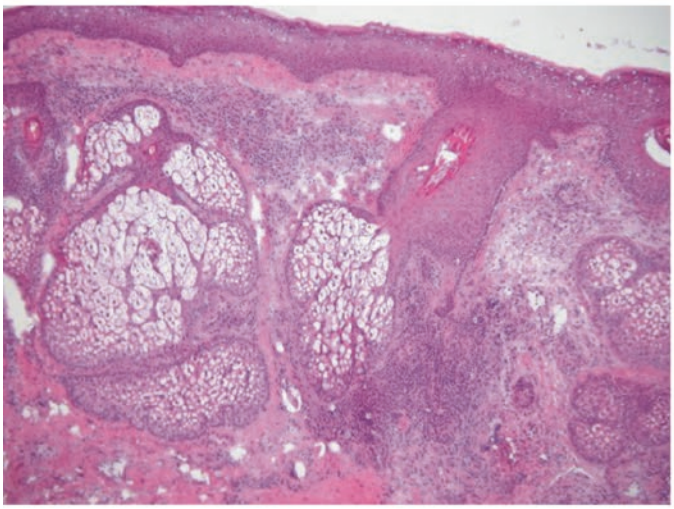
Chronic Inflammation Associated With Rosacea



LOW 3-60

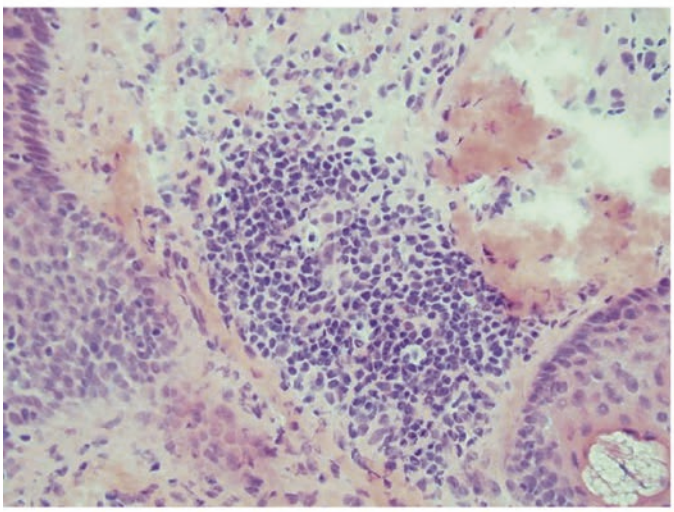
- Detail of rosacea

Note: Hypertrophied sebaceous lobules and periadnexal infiltrate



MEDIUM 3-61

- Patchy perifollicular lymphocytic infiltrate of rosacea



HIGH 3-62

- High-power photomicrograph of rosacea

Note: Follicular tropism of lymphocytic-predominant inflammatory infiltrate

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Benign Epidermal Tumors

4

Michael B. Morgan

EPIDEMIOLOGY: VV-Common, SK-Common, CCA-Uncommon.
ETIOLOGY: VV-HPV infection, SK-Unknown, CCA-Phosphorylase deficiency.
PATHOLOGY: VV-Digitate squamous proliferation with hypergranulosis and koliocytes, SK-Hyperkeratosis with acanthosis and horn cysts, CCA-Clear cell acanthosis with neutrophilic infiltration.
CLINICAL: PVV-Hyperkeratotic flat or popular neoplasm, SK-Hyperpigmented patch or plaque, CCA-Sticky papule.

There are a variety of things, including benign epidermal neoplasms, that may be discovered incidentally in the search for meaningful neoplasms or answers. These neoplasms consist of a hodgepodge of benign tumors confined to the epithelium which may occasionally evoke quandary in regard to identity or confusion with malignancy. The topics of this chapter will include verruca (VV), seborrheic keratosis (SK) and clear cell acanthoma (CCA). Other benign entities that can be so considered, including prurigo nodularis, lichen simplex chronicus and pseudoepitheliomatous hyperplasia, are discussed in the following chapter.

Verruca, whether in the guise of its most common presentation *vulgaris* or configured as the planar or plantar form, is produced by infection with the human papillomavirus (HPV). These lesions are often discovered as serendipitous lesions in the removal of cutaneous carcinoma. They typically show varying degrees of epidermal hyperplasia and papillomatosis, the common and defining histologic accompaniement being epidermal hypergranulosis and vacuolated intracytoplasmic areas known as koilocytes. The most important development relevant to the Mohs surgeon or pathologist is the presence of keratinocytic dysplasia. Following the permissive effects of ultraviolet light, through HPV-induced dysregulation of the p53 gene product or subjugated immunity as observed in renal transplant patients, significant epidermal dysplasia including squamous cell carcinoma can be encountered.

Seborrheic keratosis is an extremely common cosmetic nuisance often found in the margins of or incidentally in the examination of cutaneous tissue sections. These entities have no known association with cutaneous malignancy although they are associated with advancing age. The histology consists of epidermal acanthosis, laminated orthohyperkeratosis, basilar keratinocyte hyperpigmentation and the presence of intraepidermal micro-cysts referred to as horn cysts.

Clear cell acanthoma is an uncommon epidermal tumor of keratinocytes most commonly encountered as a solitary papule on the extremities. The pathology consists of an abrupt transition to a clonal population of optically clear cells due to the pathologic storage of glycogen resulting from an enzymatic defect in glycogen metabolism. The clear cells are often surmounted by scale-crust and neutrophils.

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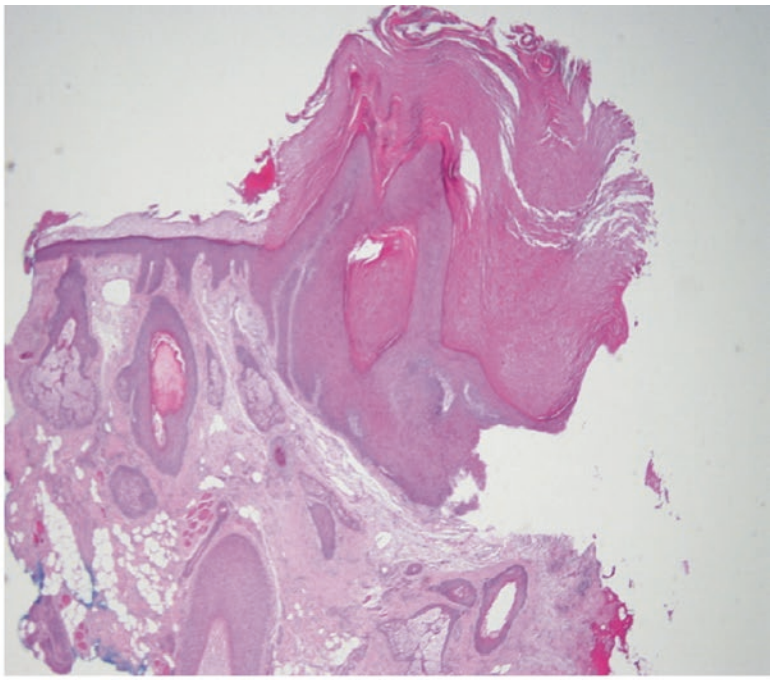
https://doi.org/10.1007/978-3-319-74847-4_4

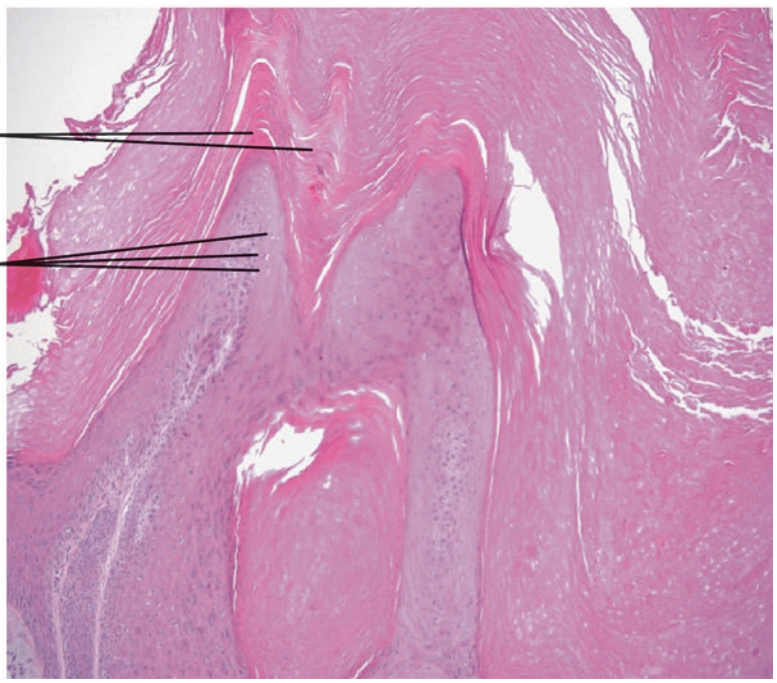
Verruca Vulgaris



VERRUCA VULGARIS *LOW* 4-1

- Discrete tumor wiht hyperker-atostic surface

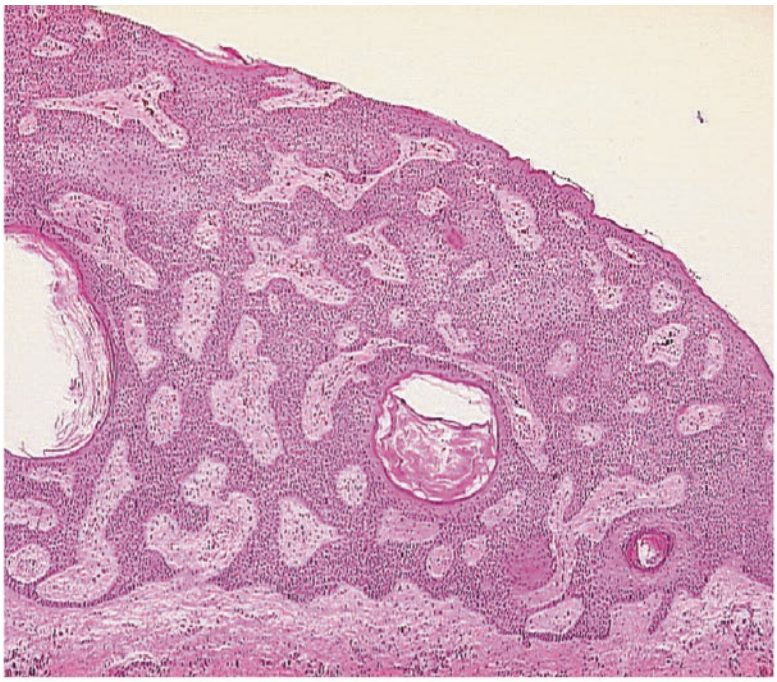
Note: Digitate configuration



VERRUCA VULGARIS *HIGH* 4-2

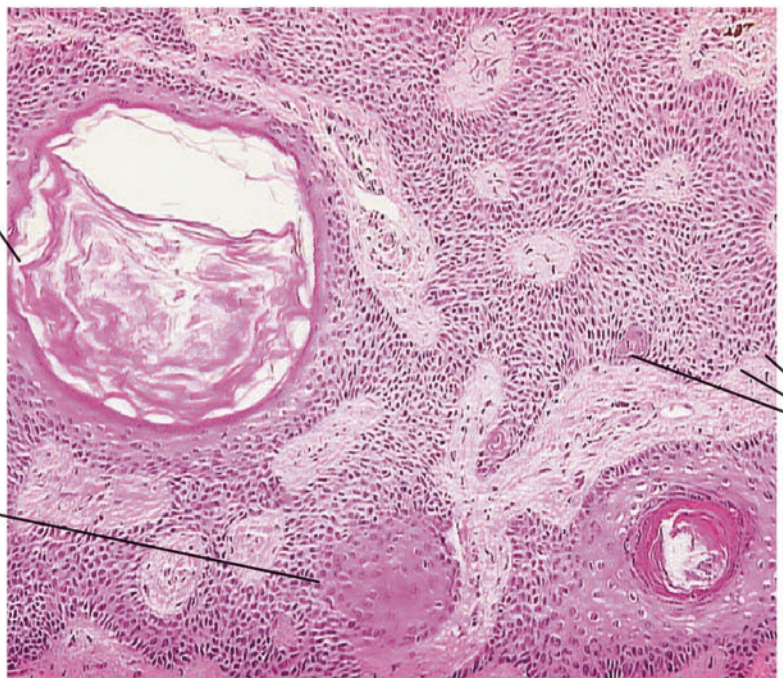
- Pointed epidermal summits with tiered cplumns of parakeratiosis

Seborrheic Keratosis



- Epidermal acanthosis with basilar hyperpigmentation

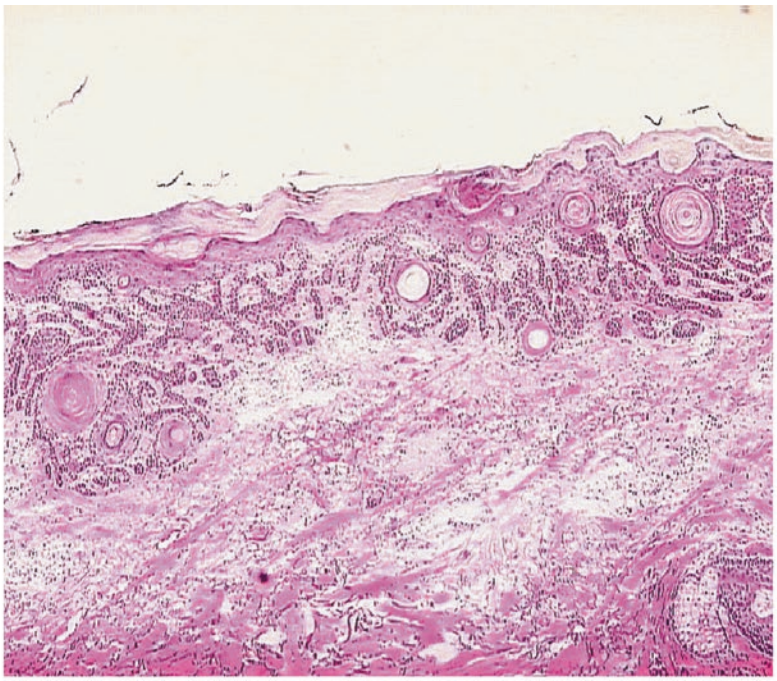
SEBORRHEIC KERATOSIS *LOW* 4-3



- High power detail on horn cysts and squamous eddies

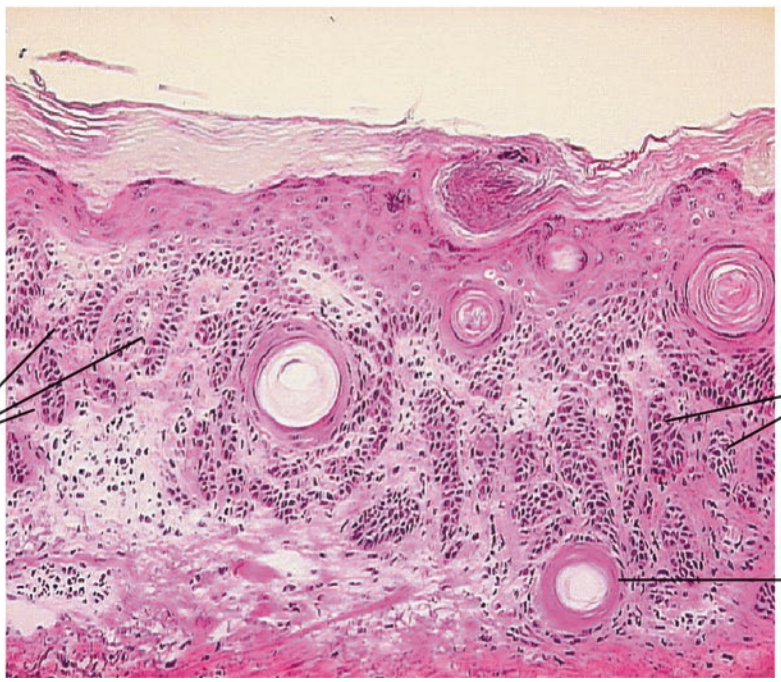
SEBORRHEIC KERATOSIS *HIGH* 4-4

Seborrheic Keratosis



- Epidermal tumor with retiform extensions

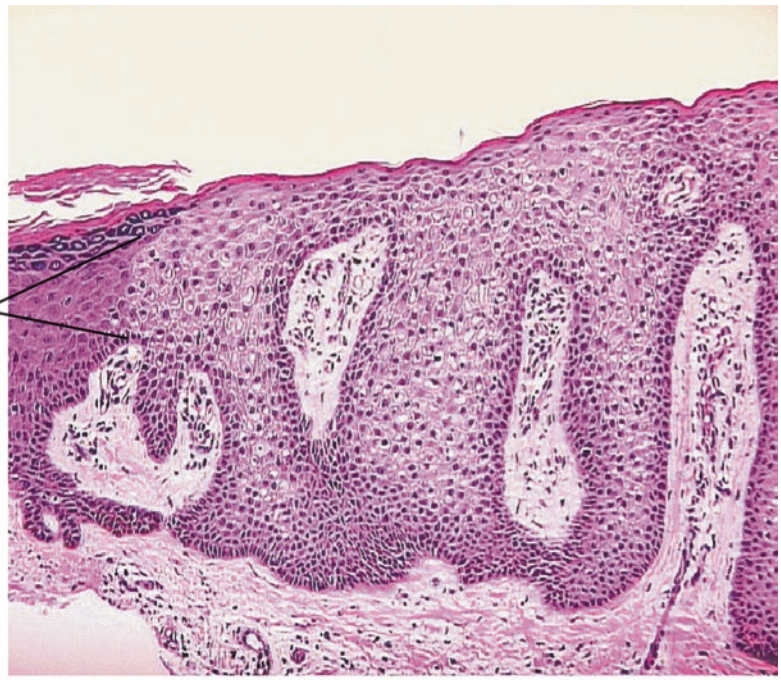
SEBORRHEIC KERATOSIS *LOW* 4-5



- High power detail of seborrheic keratosis

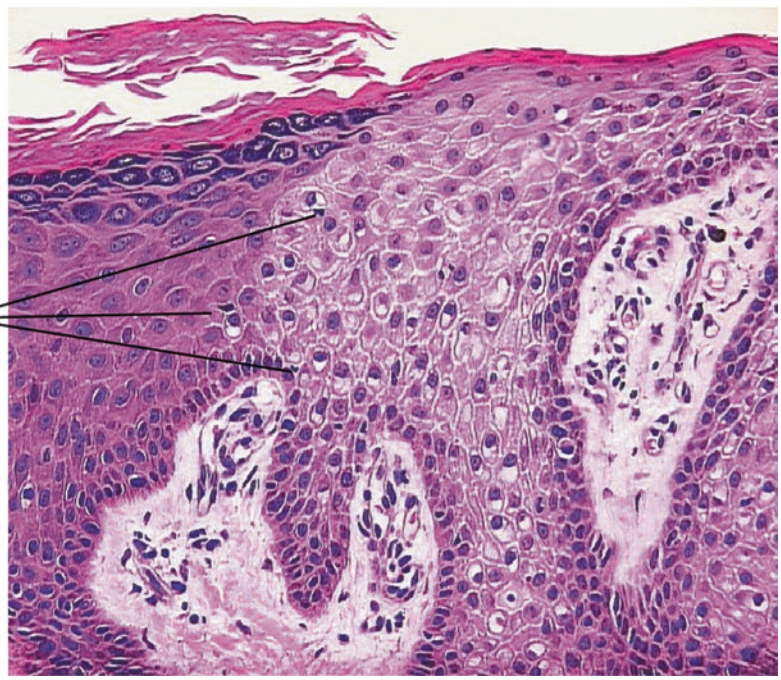
SEBORRHEIC KERATOSIS *HIGH* 4-6

Clear Cell Acanthoma



CLEAR CELL ACANTHOMA *LOW* 4-7

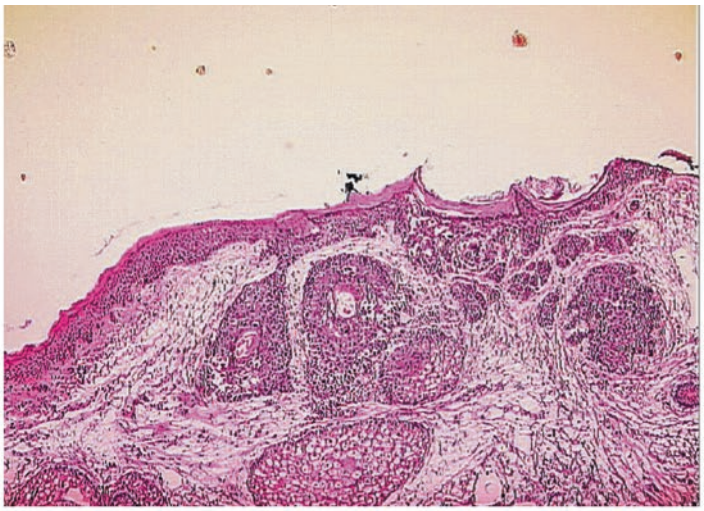
- Epidermal acanthosis with optically clear cells



CLEAR CELL ACANTHOMA *HIGH* 4-8

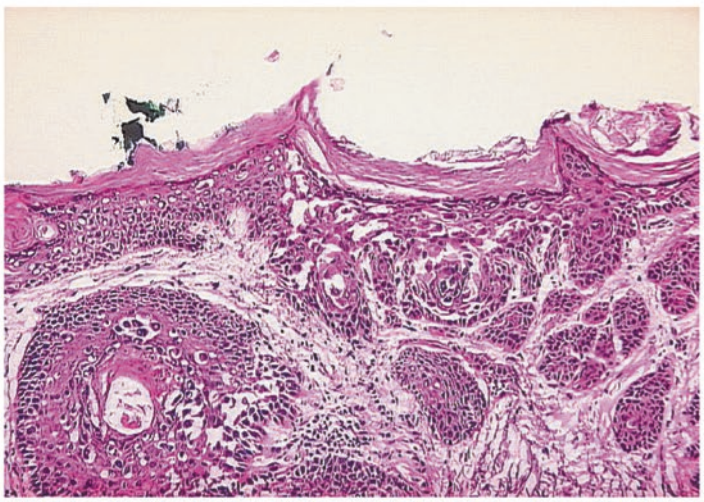
- High power detail of keratinocyte glycogenization

Warty Dyskeratoma



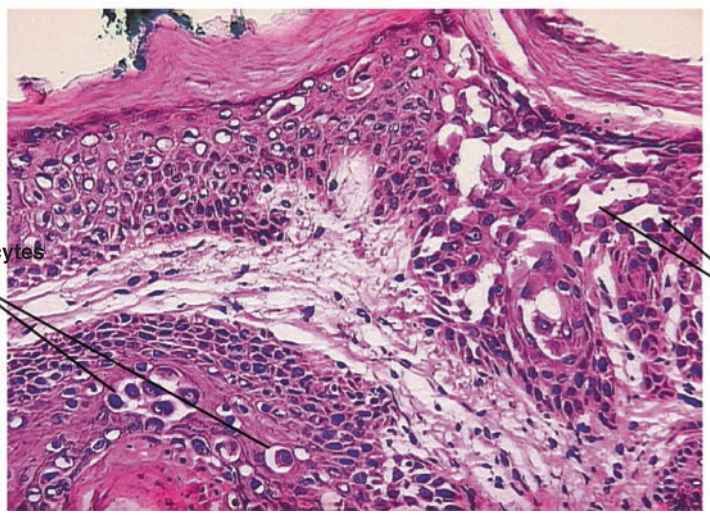
LOW 4-9

- Focal vertically oriented epithelial and follicular involvement



MEDIUM 4-10

- Acantholytic and dyskeratotic change of epithelium and adjacent follicle



HIGH 4-11

Note: Free-floating acantholytic cells

Note: Permaturely keratinized (dyskeratotic) keratinocytes

Bibliography

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Pseudotumors

5

Martin Dunn

A pseudotumor is either a non-neoplastic fluid, rich accumulation that resembles a true neoplasm, or a circumscribed cellular exudate of inflammatory origin. Normal wound healing proceeds through three well-known phases: inflammatory, proliferative and remodeling, resulting in a normal scar. Pseudotumors develop as an abnormal extension of the otherwise orderly process of wound healing. For the following discussion, pseudotumors will be presented in relation to the steps in normal wound healing.

Inflammatory

The immediate vascular response to injury of the skin is followed shortly by the inflammatory phase of wound healing, usually completed within two weeks. Inflammation persisting longer is by definition chronic inflammation. Granulocytes have decreased or disappeared, while lymphocytes, monocytes and macrophages increase in number. Macrophages attract fibroblasts, which over time produce increased amounts of collagen. The resulting encapsulated mass, the granuloma, is considered the body's last defense. Chronic inflammation may be associated with tissue contaminated by pathogens and/or insoluble foreign material. Granulomas may also be hiding the tumor cells they are unable to destroy. (Challenge: Chronic inflammation vs. lymphoepithelioma-like SCC)

Proliferative

In the proliferative phase of wound healing re-epithelialization, angiogenesis and fibroplasia occur. Re-epithelialization of wounds begins within 24 hours following an injury. Initial epidermal cell migration is followed by proliferation. Proliferation may be excessive, a condition known as hyperplasia. Psoriasiform hyperplasia is the term used when there is regular acanthosis resembling psoriasis. Pseudoepitheliomatous hyperplasia (PEH) is extreme epidermal proliferation that simulates well-differentiated SCC. Syringosquamous metaplasia is part of the expression of PEH. (Challenge: PEH vs. well-differentiated SCC)

PEH occurs at the edges of ulcers and healing wounds. It is associated with chronic inflammatory conditions such as hypertrophic lichen planus, verrucous lupus erythematosus, chronic arthropod bites and others. Often the only way to identify PEH with certainty is to identify the underlying condition. Both lichen simplex chronicus and prurigo nodularis may have associated psoriasiform hyperplasia or PEH.

The other two parts of the proliferative phase of wound healing, angiogenesis and fibroplasia, are exemplified by granulation tissue. New vessels migrate into the wound as well as fibroblasts and ground substance. The fibroblast in particular performs multiple roles in wound healing leading to phenotypic changes in the cell over time. (Challenge: Granulation tissue vs. chronic peritumoral inflammation)

Remodeling

The third phase of wound healing consists mainly of deposition and remodeling of collagen. Initial disorganized Type III collagen is degraded and resynthesized into Type I collagen. Eventually, normal wound healing results in a scar. Usually

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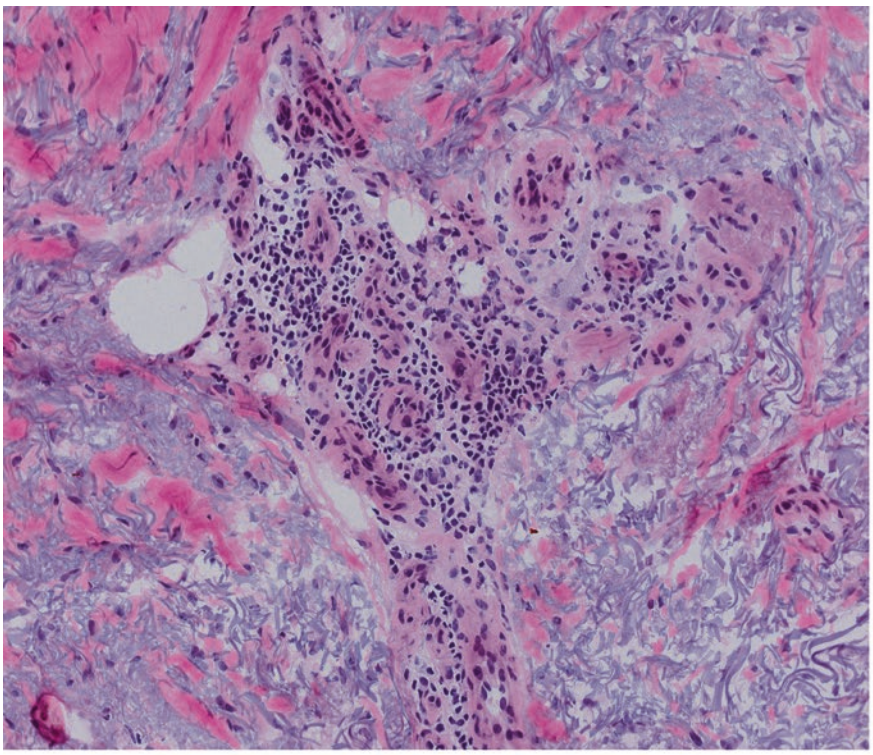
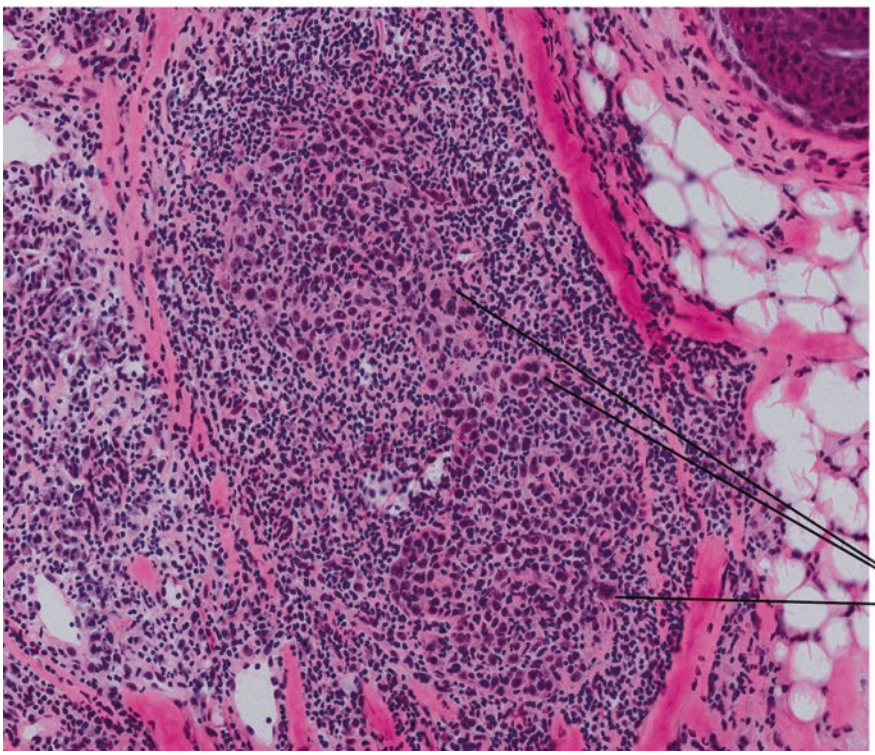
after five weeks, collagen is present in thick hyaline bundles in parallel arrangement. In both hypertrophic scars and keloids new collagen formation is slower than normal wound healing. Early in the remodeling phase collagen fibers are arranged in whorls and nodules. Hypertrophic scars gradually resolve over time. Keloids extend beyond the confines of the original wound and usually protrude prominently above the surrounding skin. Keloids contain more markedly thickened and hypereosinophilic collagen bundles, with few adnexal structures. Distinct nodules containing myofibroblasts are more characteristic of hypertrophic scars than of keloids. In both, the overlying epidermis is normal or flattened. (Challenge: Keloid vs. scar associated with recurrent SCC)

Challenge
Chronic Inflammation vs. Lymphoepithelioma-like SCC



CHRONIC INFLAMMATION 5-1

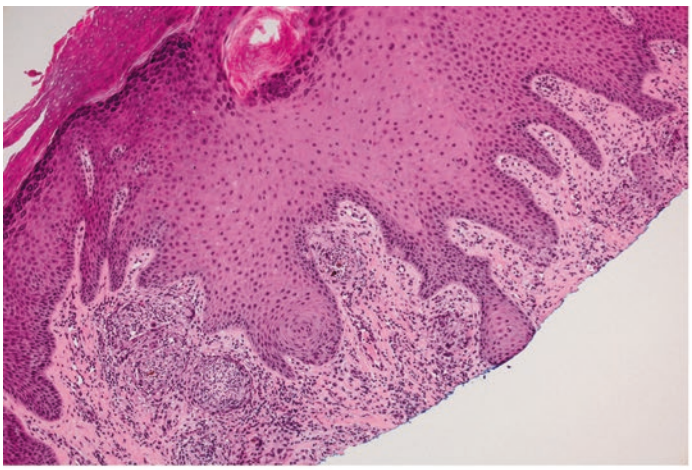
- Thickened blood vessels characteristic of the lower extremity, along with a lymphoid infiltrate, simulate tumor cells seen below



LYMPHOEPITHELIOMA-LIKE SCC 5-2

- Tumor cells are multinucleated forming expansive islands, with variation in size and shape of the cells

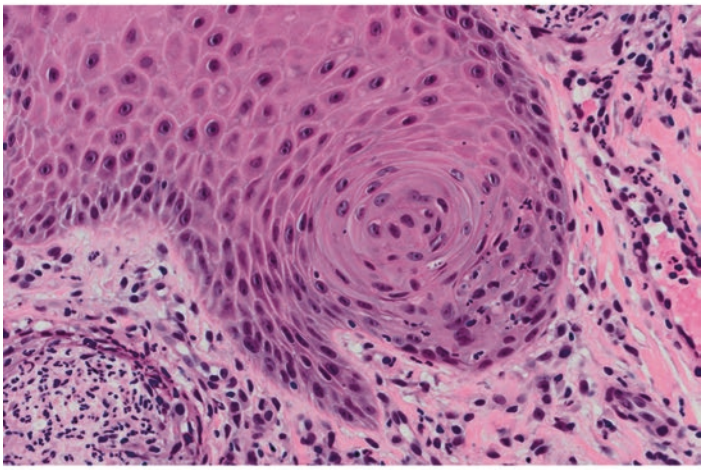
Challenge
Pseudoepitheliomatous Hyperplasia (PEH) vs. Well-differentiated Squamous Cell Carcinoma (SCC)



PEH *LOW* 5-3

- Uneven, jagged epidermal cell masses that may extend below the level of the sweat glands

Note: Vertical orientation connects with the epidermis

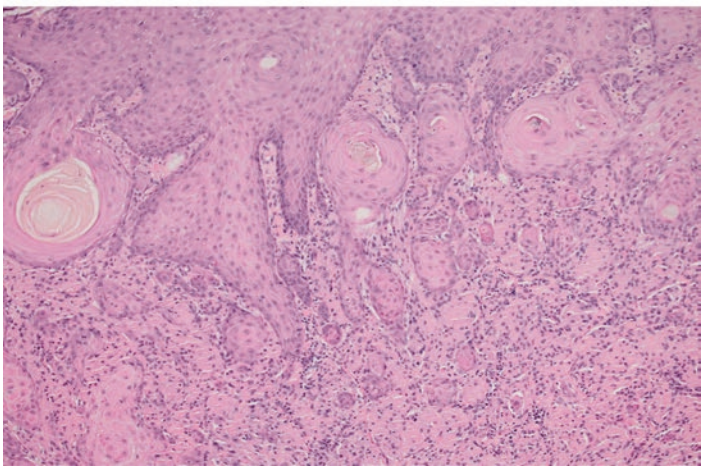


PEH *MEDIUM* 5-4

- Prominent leukocytes in the epidermal proliferation

Note: Rounded epidermal cell masses

Note: Lack of dyskeratosis, mitotic figures

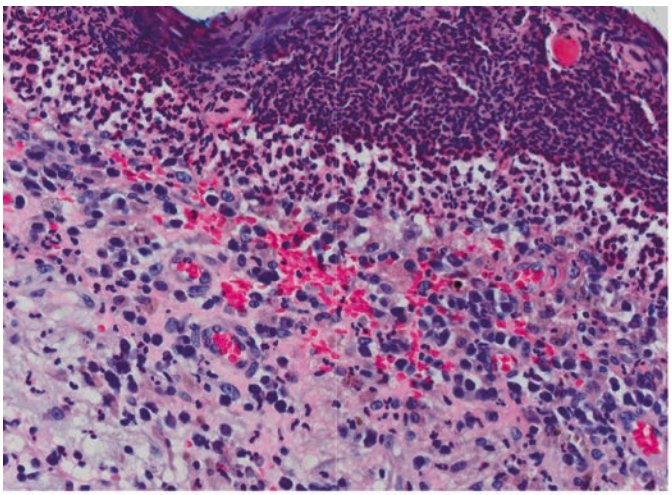


WELL-DIFFERENTIATED SCC 5-5

- Pointed, jagged and irregular epidermal extensions. Individual cell keratinization (dyskeratosis), nuclear hyperchromasia

Note: Absence of leukocytes in the tumor nests
Presence of disconnected islands of tumor in the papillary and reticular dermis

Challenge
Granulation Tissue vs. Chronic Peritumoral Inflammation

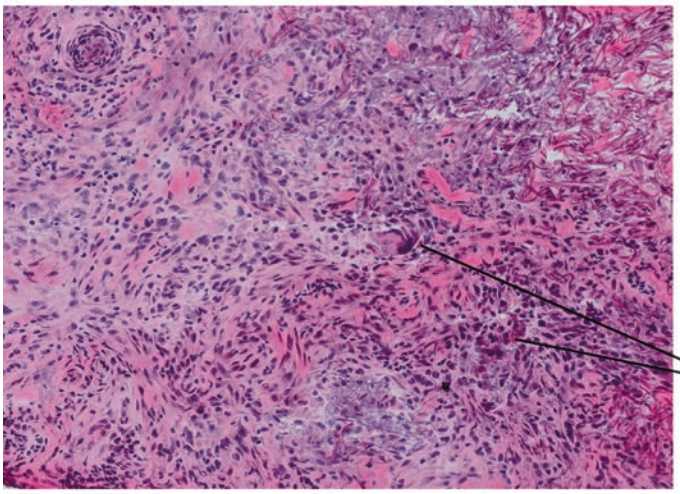


GRANULATION TISSUE SURFACE 5-6

- Admixture of both acute and chronic inflammatory cells

Note: Prominent scale-crust

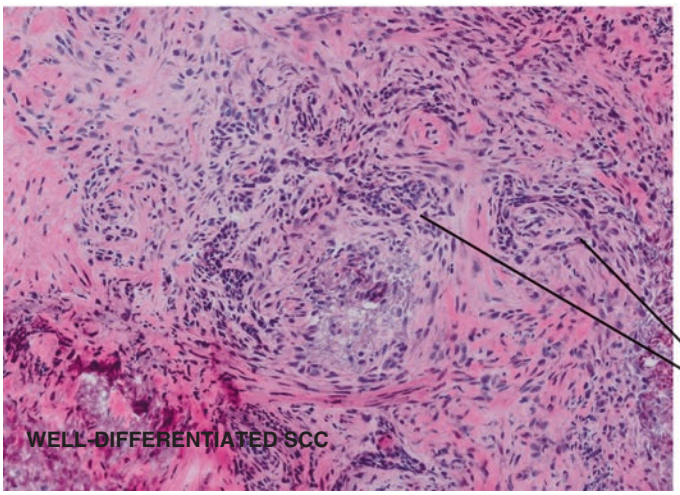
Note: Prominent new blood vessel information



SCAR WITH FOREIGN BODY GIANT CELL REACTION 5-7

- Prominent fibroblasts, ground substance and foreign body type giant cell

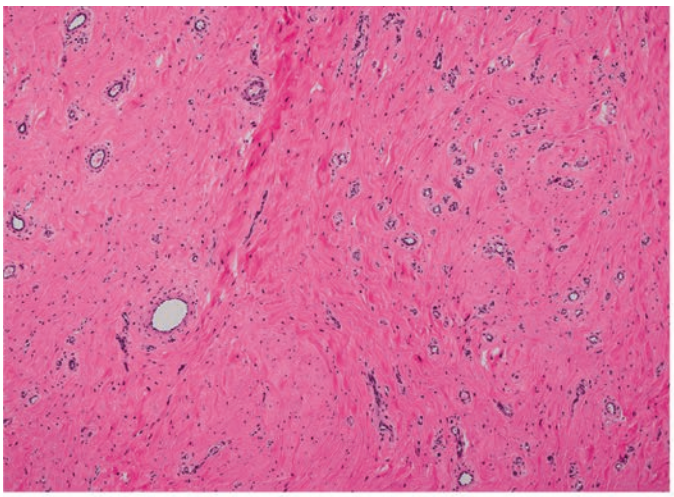
Note: Haphazard orientation



5-8

- Next section deeper into the specimen reveals nests of infiltrating BCC not apparent in the view above

Challenge
Keloid vs. Desmoplasia Associated with Morpheaform BCC

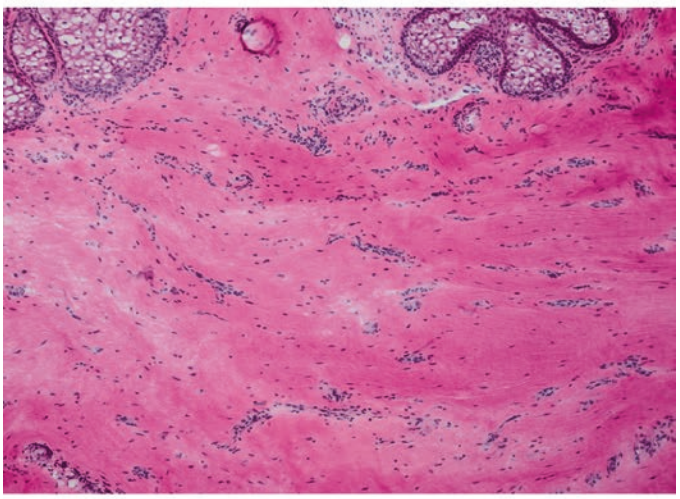


5-9

- Deep dermis with thickened hypereosinophilic collagen bundles arranged in sweeping fascicles

Note: Few adnexal structures

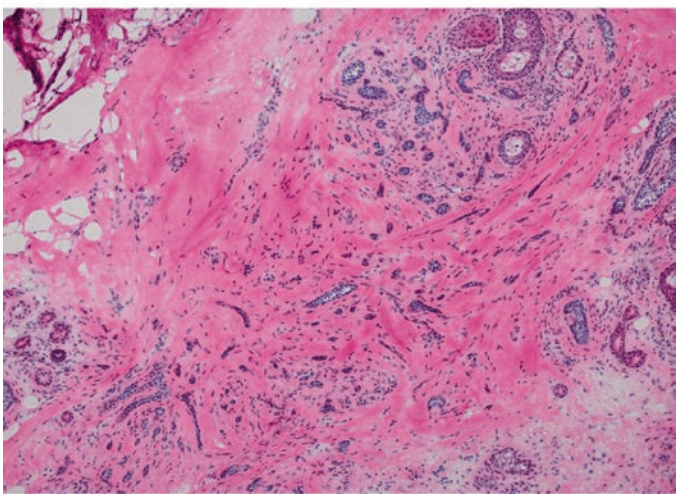
Note: Increased vascularity



5-10

- Thick bundles of deep dermal collagen arranged in fascicles

Note: Superficial adnexal structures intact



5-11

- Nests of morpheaform BCC in deep dermis infiltrating bundles of collagen

Note: Deep dermal adnexal stuctures intact

Note: Normal vascular pattern

Note: Absence of scar
(sweeping fascicles of collagen)

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Squamous Cell Carcinoma: Variants and Challenges

6

Michael B. Morgan

EPIDEMIOLOGY: Second most common skin cancer, rare in the dark-skinned races.
ETIOLOGY: Ultraviolet light, HPV infection.
PATHOGENESIS: p53 tumor suppressor gene mutation.
CLINICAL: Rapidly growing keratotic papule or shallow ulcer in sun-exposed site of elderly.
HISTOLOGY: In situ lesions with full thickness or pagetoid scatter of dysplastic keratinocytes, invasive infiltrating keratinizing neoplasm may be **pigmented**, **warty (verrucous)**, **acantholytic**, heavily inflamed (**lymphoepithelioma**) or **spindled.**

Squamous cell carcinoma (SCC) is the second most frequent form of skin cancer superseded by only basal cell carcinoma. Like basal cell carcinoma, SCC is predisposed for by excessive ultraviolet exposure, hence its association with advancing age and cumulative sun exposure, exposed anatomic sites and highest incidence in sunny geographic locales. The most important pathogenic mechanisms involve aberration of the p53 tumor suppressor gene via ultraviolet-induced mutation or HPV-encoded interdiction. The latter mechanism is thought to be the most important factor in the development of these malignancies in the setting of epidermodysplasia verruciformis and solid organ iatrogenic immunosuppression where multicentric tumor may present in a metachronous or synchronous fashion. Less common associations have been ascribed to chronic inflammatory or scarring conditions such as in the setting of burns, so called Marjolin's ulcer, osteomyletic sinuses and lichen sclerosis et atrophicus, among others. The typical clinical presentation entails a rapidly growing keratotic papule or shallow ulcer on an exposed anatomic site in the elderly. These tumors may be broadly divided into intraepithelial malignancy and invasive tumors.

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The intraepithelial form synonymously referred to as Bowen's disease or squamous cell carcinoma-in-situ, may histologically present in the guise of transepidermal keratinocytic dysplasia or as scattered dysplastic (pagetoid) keratinocytes found throughout all levels of the epithelium and extending into adjacent adnexal epithelium. These forms of the disease may exist in continuity with focal keratinocytic dysplasia confined to the basilar layer of the epithelium (actinic keratosis) or focal to full-thickness dysplasia without adnexal extension (bowenoid actinic keratosis). The relationship of these lesions to squamous cell carcinoma remains contentious, particularly in regard to their potential as precursors of SCC. Invasive squamous carcinoma can be histologically and prognostically stratified. Prognostic subcategorization can be accomplished on the basis of their degree of differentiation (well, moderate and poor) with increasing de-differentiation representative of a worse prognosis. Additional prognostic attributes that may be sought after include the depth of dermal invasion, the presence of vascular permeation or perineural extension. Deeper dermal extension, vascular permeation and perineural involvement have all been shown to portend a worse outcome. Histologic variants include a pigmented form associated with benign intra-tumoral melanocytes, an acantholytic form with dyshesive neoplastic keratinocytes, a spindled form which may be readily confused with melanoma or other spindled tumors, a lymphoepithelioma type with a rich endowment of lymphocytes, and a warty-like verrucous variant.

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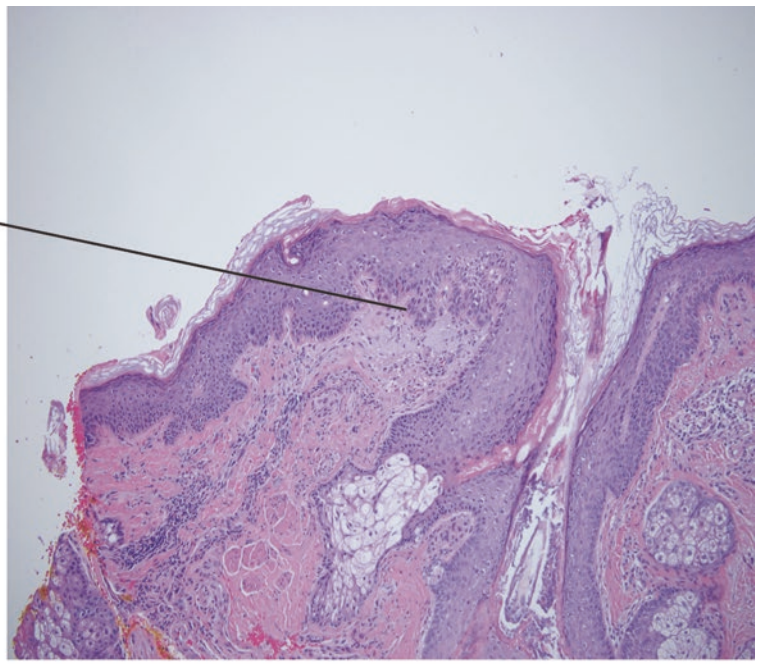
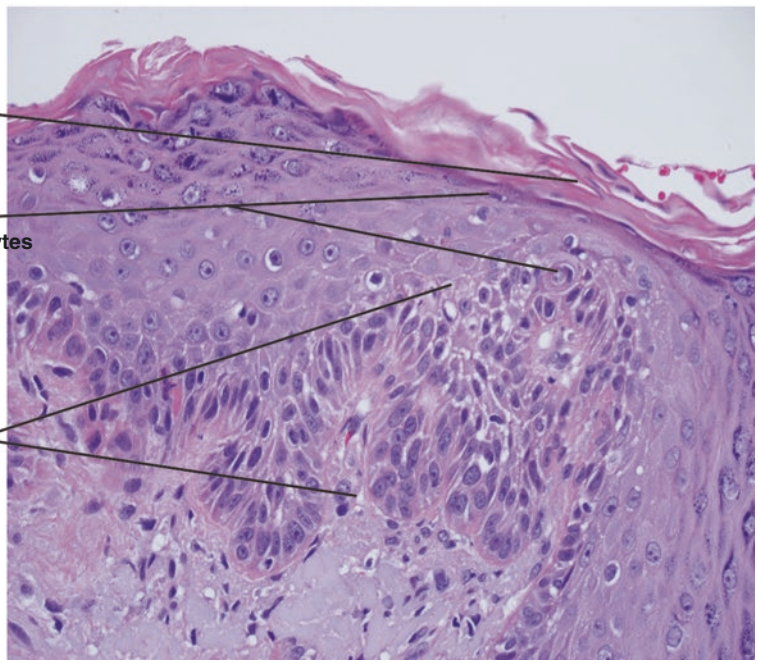
https://doi.org/10.1007/978-3-319-74847-4_6

Precursor Lesion
Actinic Keratosis (AK)



MEDIUM 6-1

- Focal keratinocyte dysplasia confined to the basilar area of the epithelium



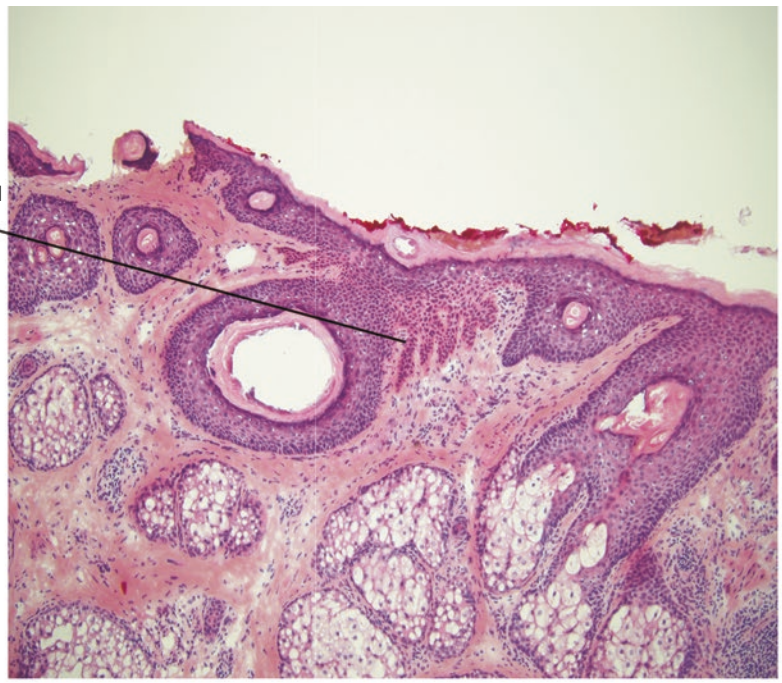
HIGH 6-2

- Dysplasia defined by enlarged hyperchromatic keratinocyte nuclei

Note: surface keratinocyte maturation

Note: Focal parakeratosis overlying dysplastic foci

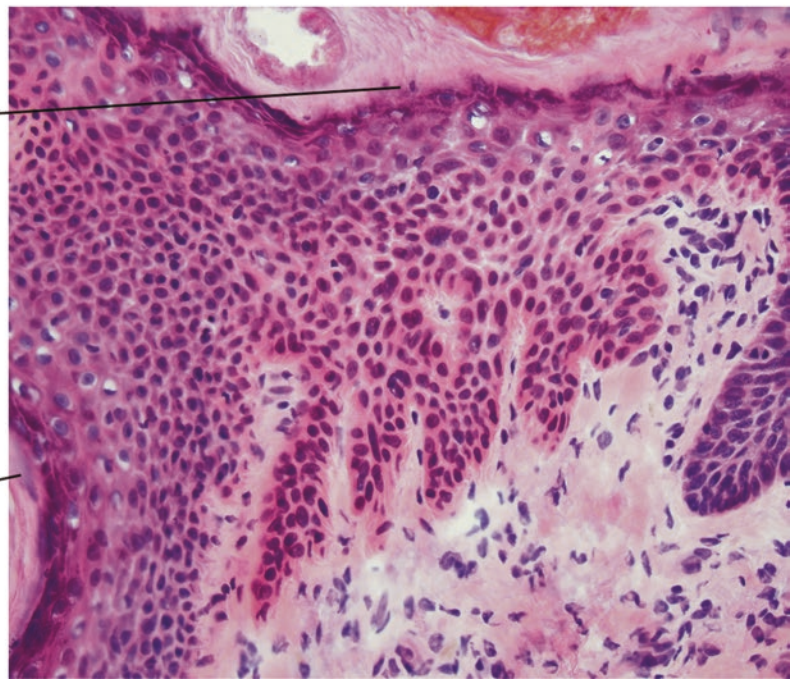
Precursor Lesion
Bowenoid Actinic Keratosis



MEDIUM 6-3

- Focal full thickness dysplasia

Note: Eosinophilia of cytoplasm (Dyskeratosis)

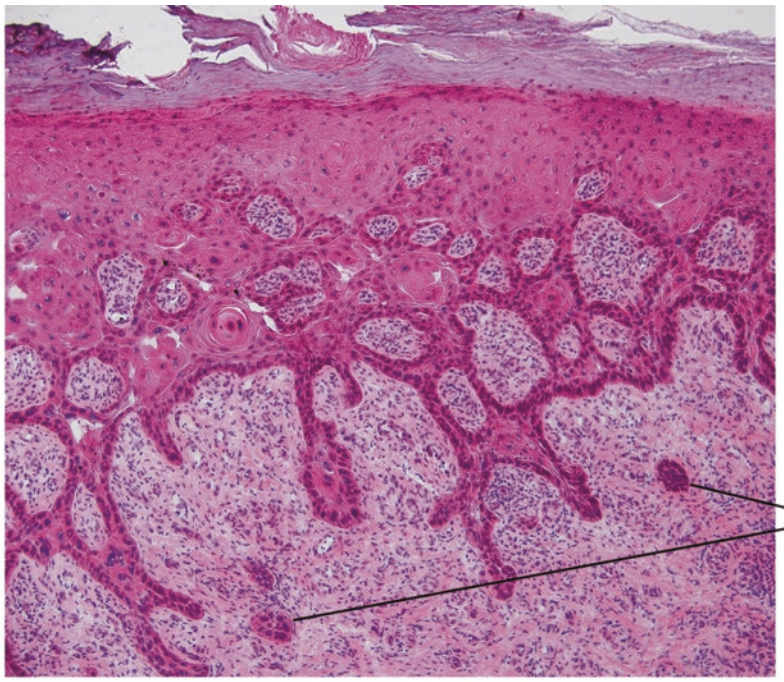


HIGH 6-4

- Dysplastic keratinocytes defined by hyperchromatic enlarged nuclei
- No extension down adjacent follicle

Note: Parakeratosis

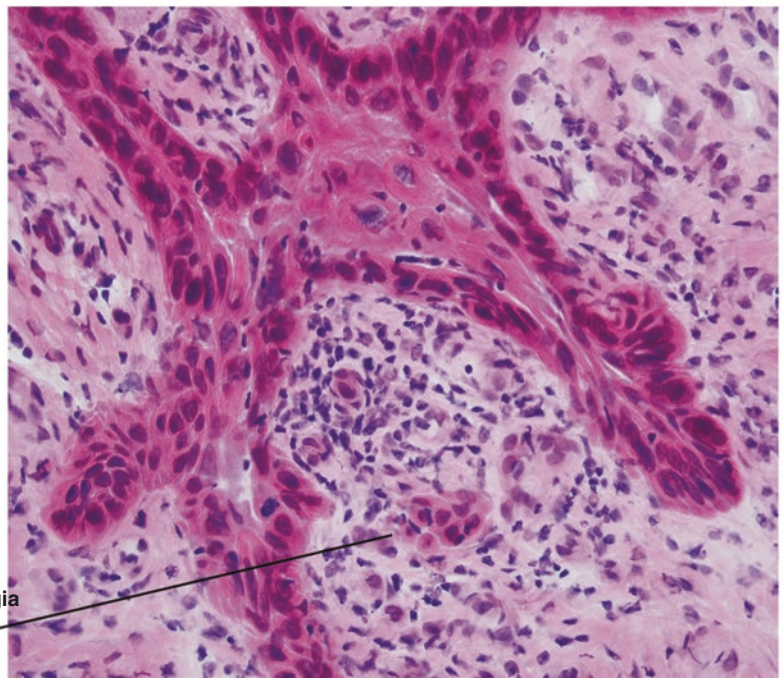
Squamous Cell Carcinoma In-Situ



- Transepidermal keratiniocyte dysplasia
- Extension down adnexal structures, (Acrosyringia)

Eccrine ducts (Acrosyringia)

MEDIUM 6-5

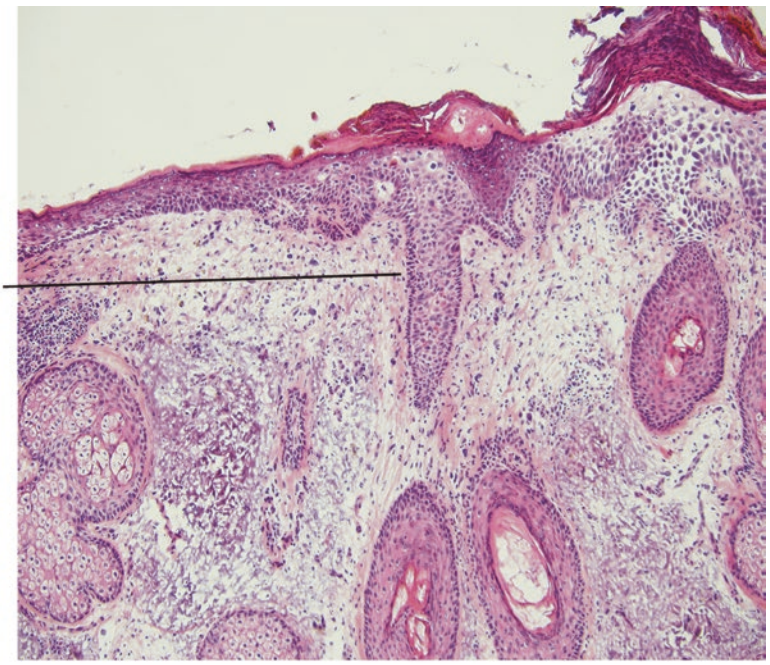


Acrosyringia

- Eccrine (Acrosyringeal) extensions

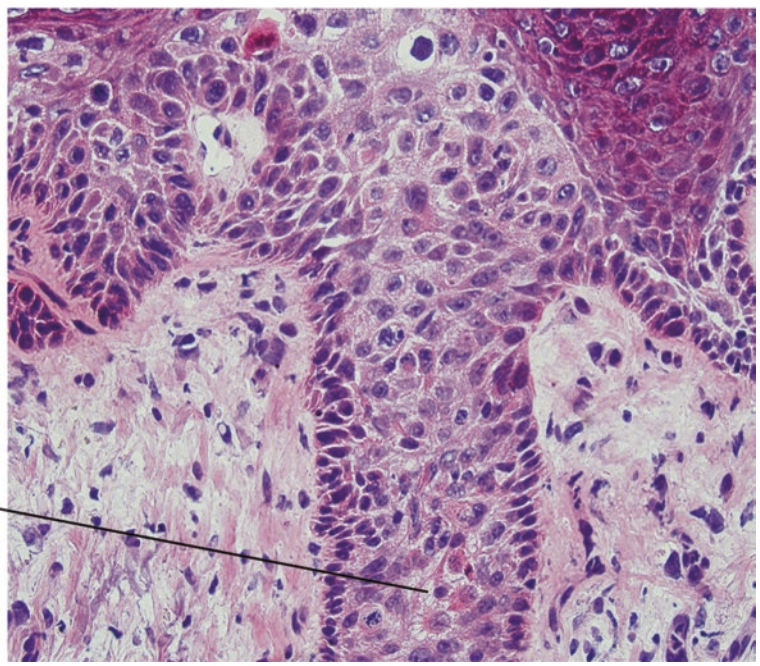
HIGH 6-6

Variants
Squamous Cell Carcinoma In-Situ with Follicular Extension



MEDIUM 6-7

- SIS with follicular extension

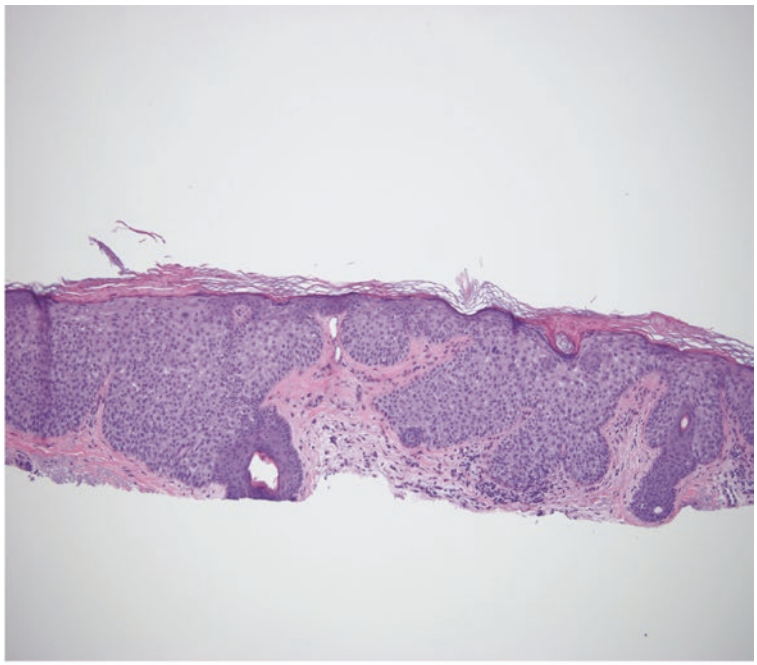


HIGH 6-8

- Follicle effaced by dysplastic keratinocytes

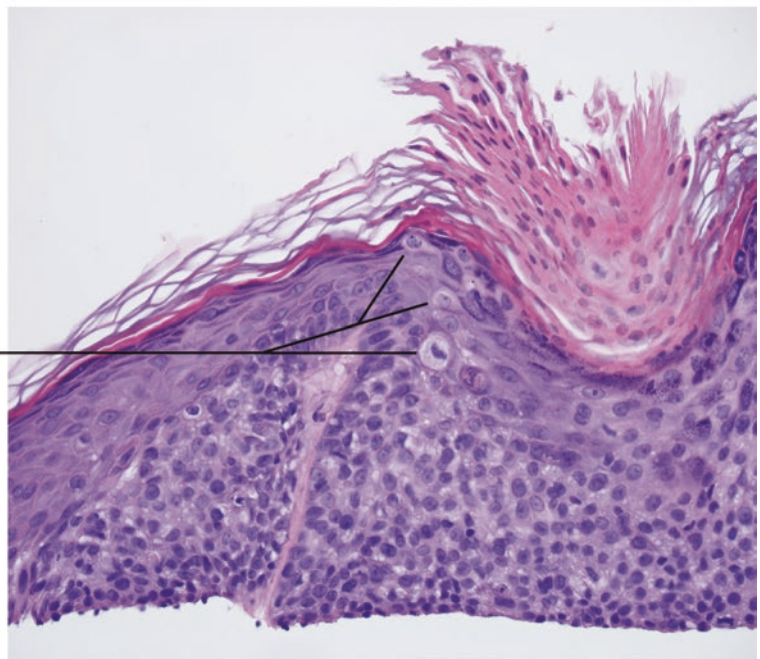
Note: Dyskeratosis

Clear Cell Bowens Disease



- Multifocal transepidermal dysplasia

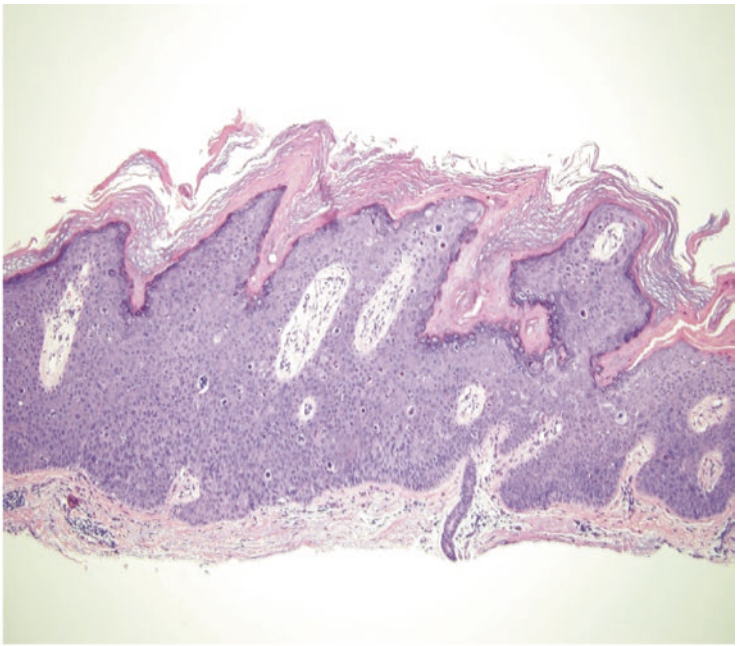
MEDIUM 6-9



Note: Cytoplasmic pallor (clear cells)
Note: Pagetoid scatter of dysplastic keratinocytes

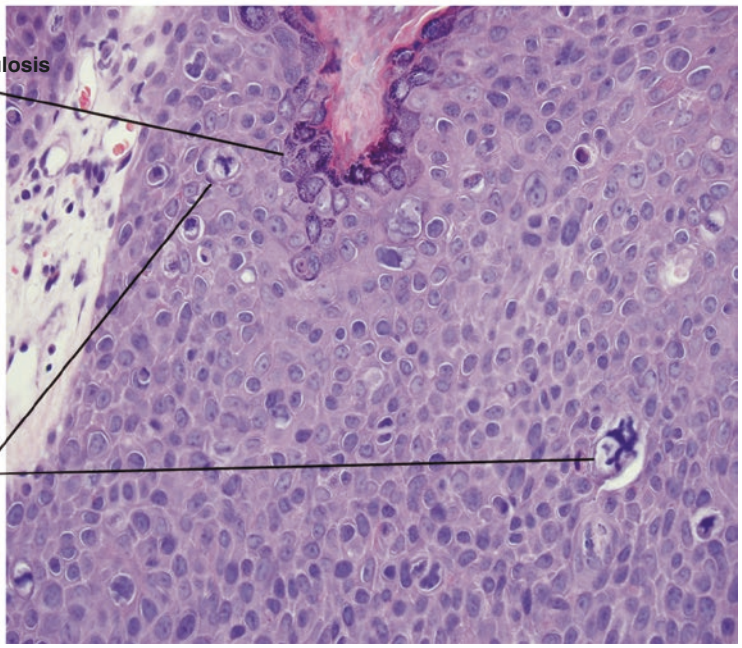
HIGH 6-10

SCC-In-Situ Arising in Verruca (HPV Effect)
Bowens Disease



- Warty silhouette
- Transepidermal keratinocyte dysplasia

MEDIUM 6-11

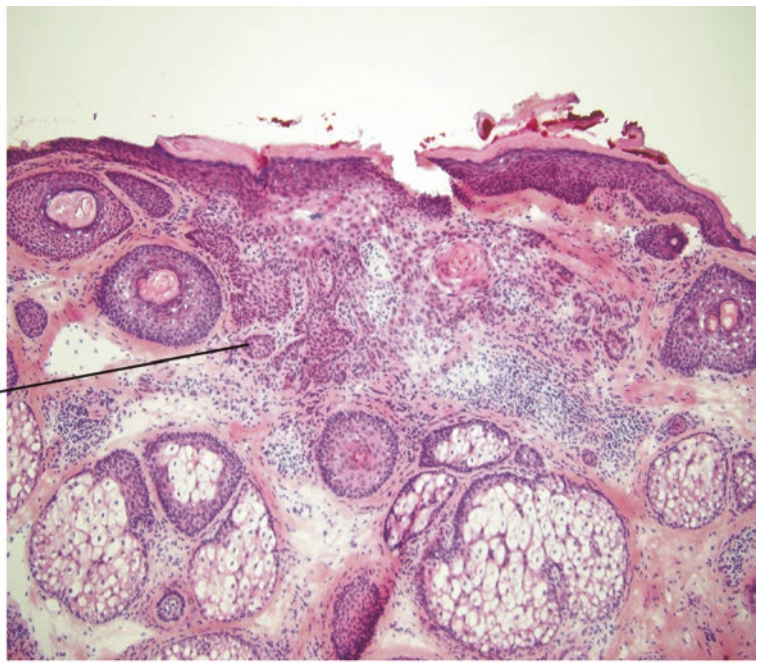


- Hypergranulosis (HPV effect)

Note: Severe dysplasia and atypical mitotic figures

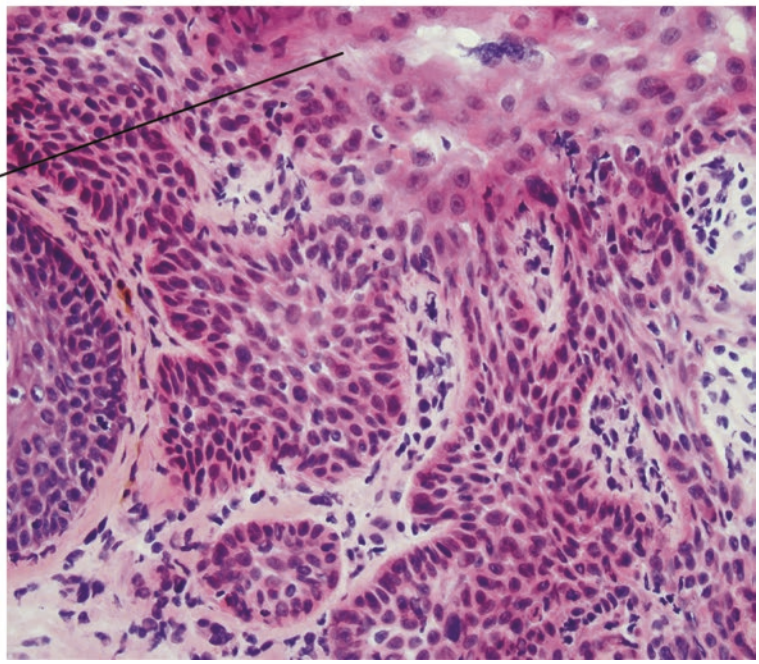
HIGH 6-12

Variants
Microinvasive Well-differentiated SCC



MEDIUM 6-13

- Irregular infiltration by SCC confined to superficial dermis

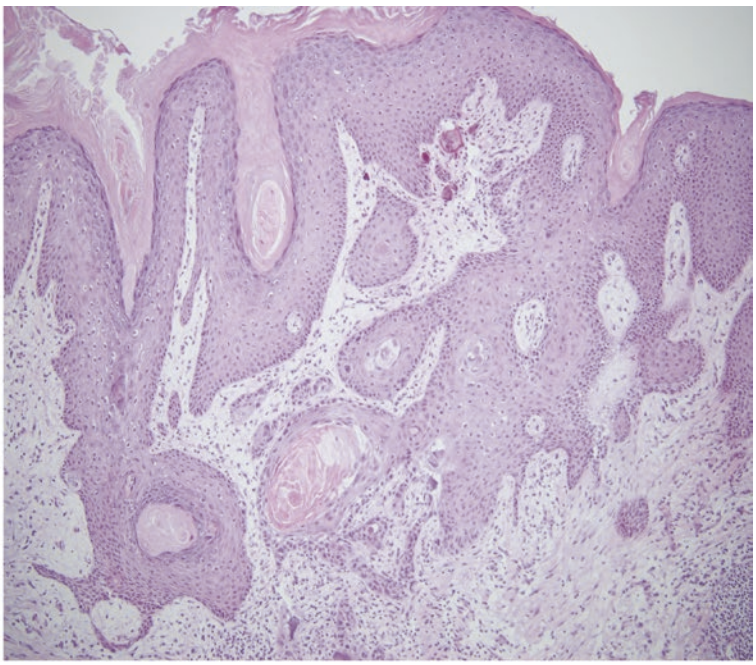


HIGH 6-14

- Irregular infiltration defined by jagged silhouette

Note: Coarse parakeratosis

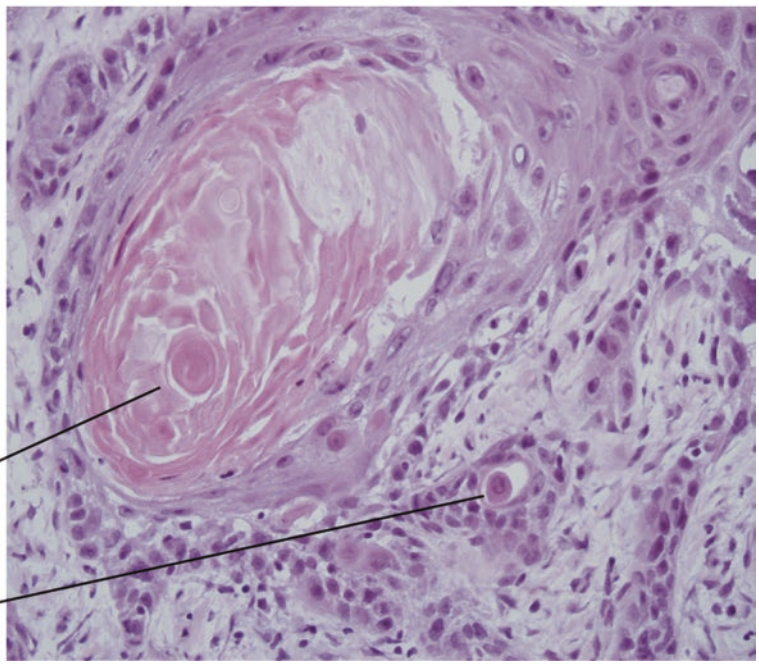
Histologic Grade
Well-differentiated SCC



MEDIUM 6-15

- Invasive well-differentiated SCC

Note: Irregular infiltrating foci

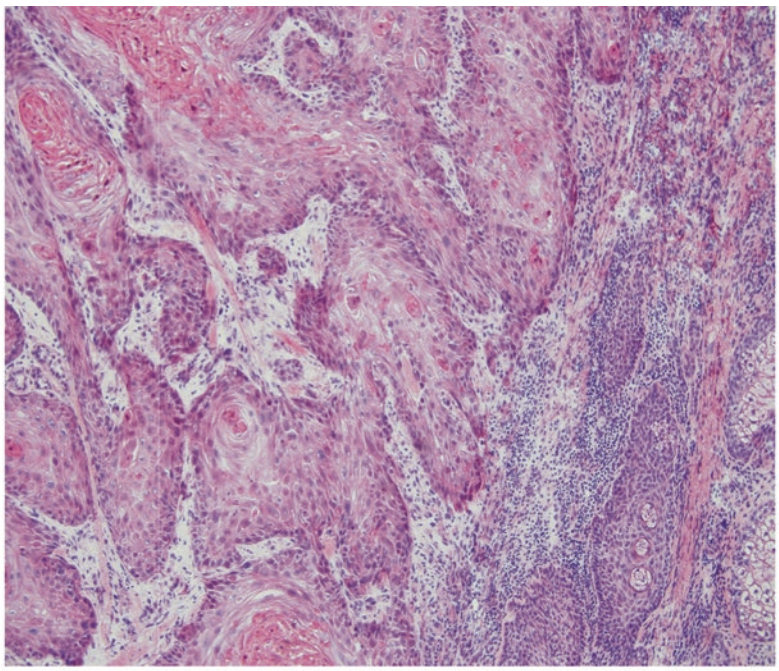


HIGH 6-16

- Well-differentiated SCC with dysplastic keratinocytes

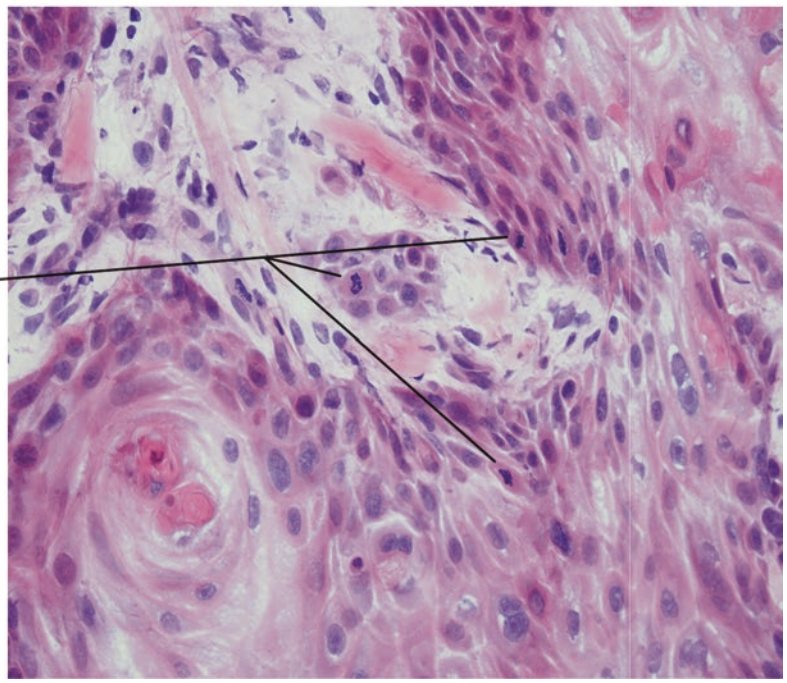
Note: Squamous pearls and dyskeratosis

Histologic Grade
Moderately Differentiated SCC



MEDIUM 6-17

- Irregular infiltrating SCC



Mitosis

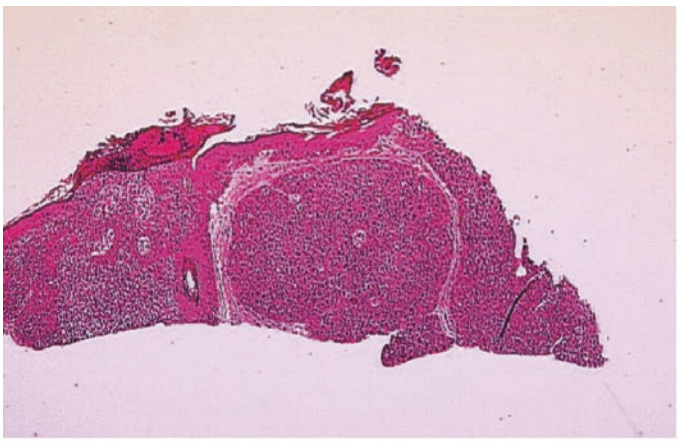
HIGH 6-18

- Moderate degree of differentiation

Note: Enlarged nuclei with altered nuclear/cytoplasm ration

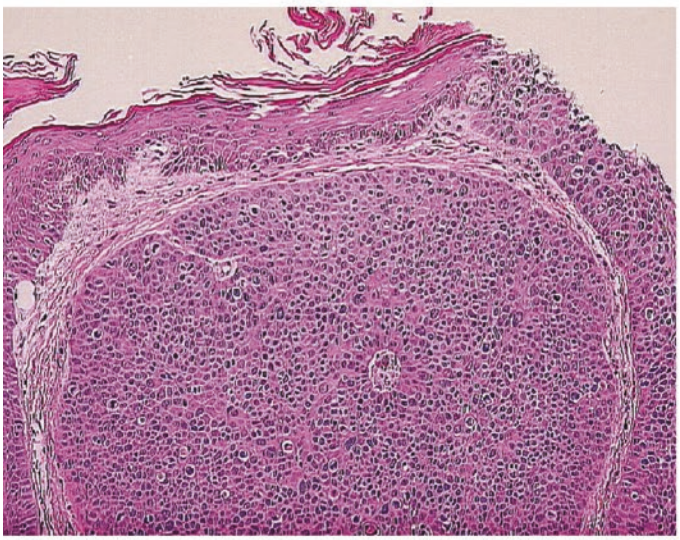
Note: Scattered mitosis

Histologic Grade
Poorly Differentiated SCC



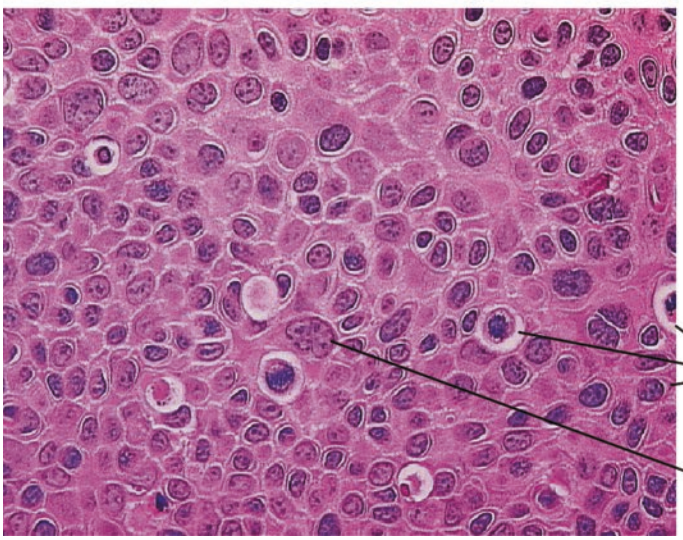
LOW 6-19

- Irregular nodular expansion of epithelium



MEDIUM 6-20

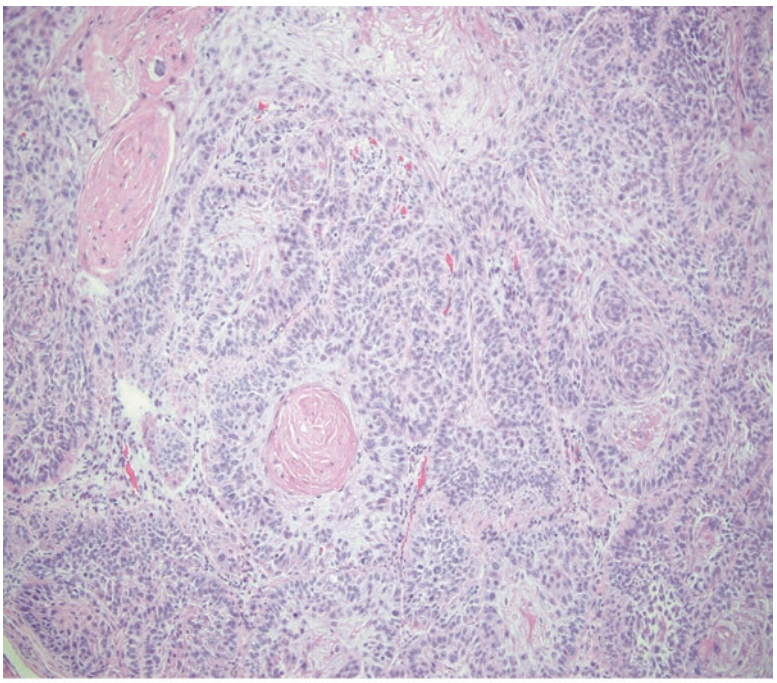
- Detail of squamous tumor with superficial parakeratosis and underlying nodular growth



HIGH 6-21

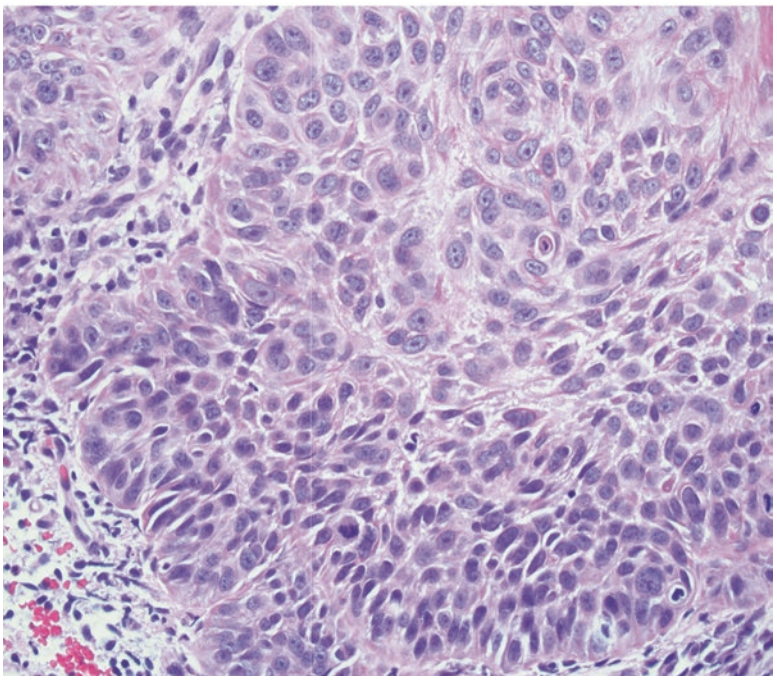
- Detail of non-keratinizing meno-and multinucleate cells with dyskeratosis and increased number of mitosis

Histologic Grade
Poorly Differentiated SCC



MEDIUM 6-22

- Irregular infiltrative neoplasm with keratinized foci



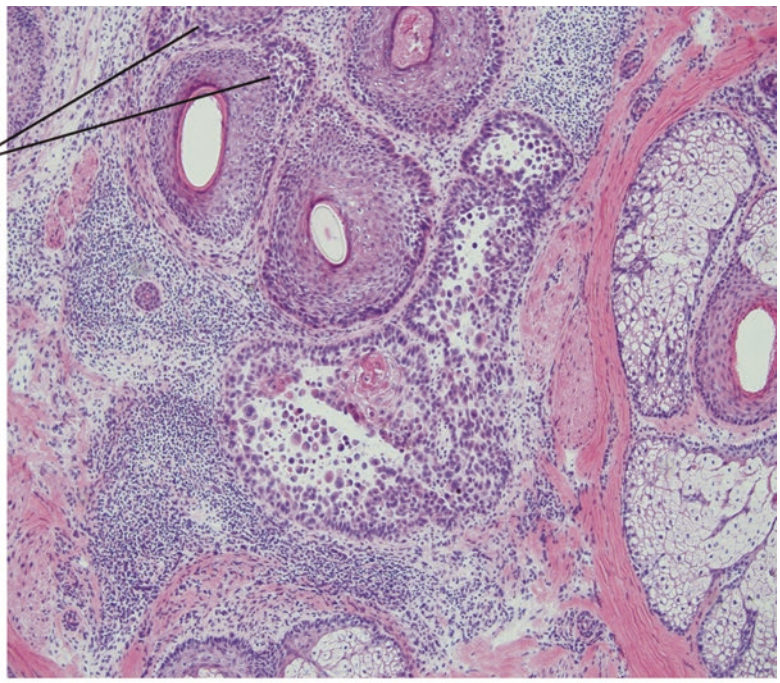
HIGH 6-23

- Detail of a poorly differentiated SCC

Note: High Nuclear/Cytoplasmic Ratio

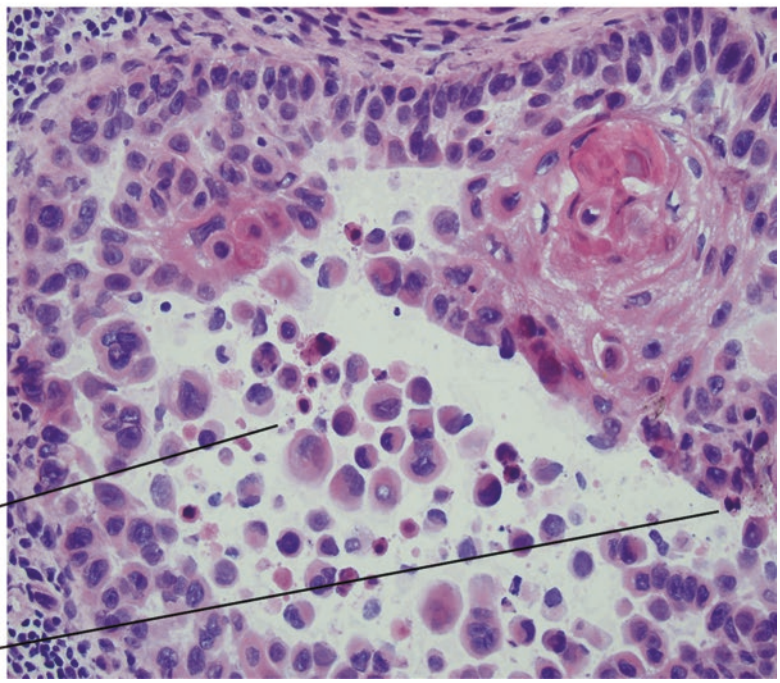
Note: Hyperchromatic enlarged nuclei

Variants
Acantholytic SCC



MEDIUM 6-24

- Acantholytic SCC seen within dermis and extending around follicle



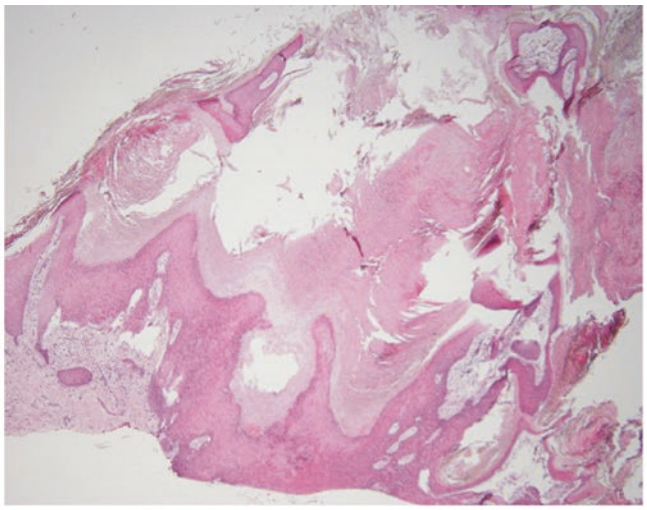
HIGH 6-25

- Acantholysis defined by dyshesive keratinocytes

Note: Free floating keratinocytes forming a cavity

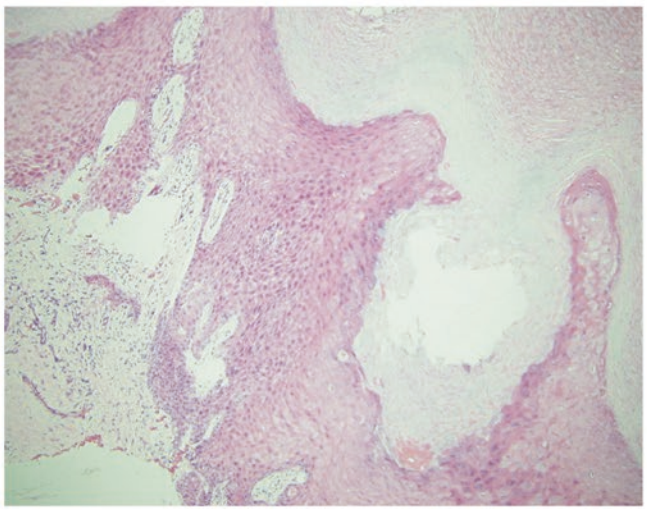
Note: Dyskeratosis and mitotic figures

Keratoacanthoma Type Squamous Cell Carcinoma



LOW 6-26

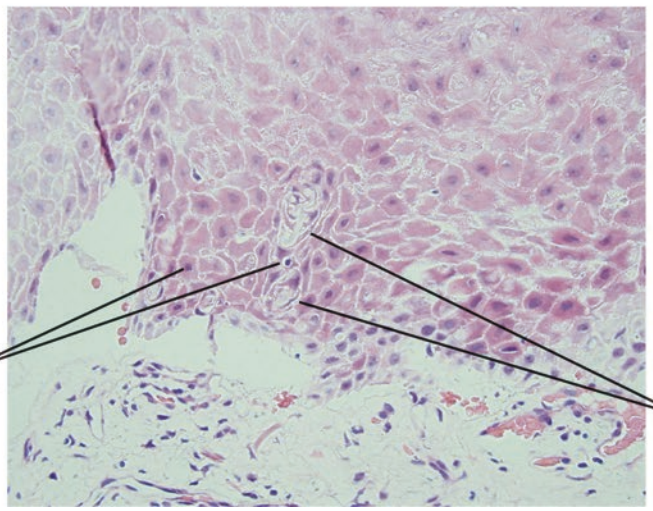
- Endophytic neoplasm with hyperkeratosis and digitate epidermal extensions



MEDIUM 6-27

- Detail of digitate extensions

Note: Irregular dermal extensions

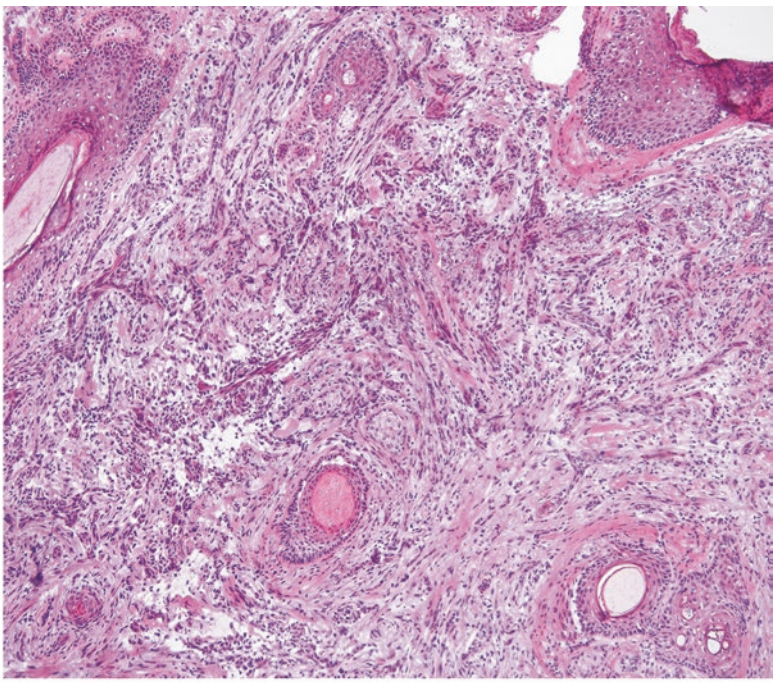


HIGH 6-28

- High power showing epidermal keratinocyte pallor

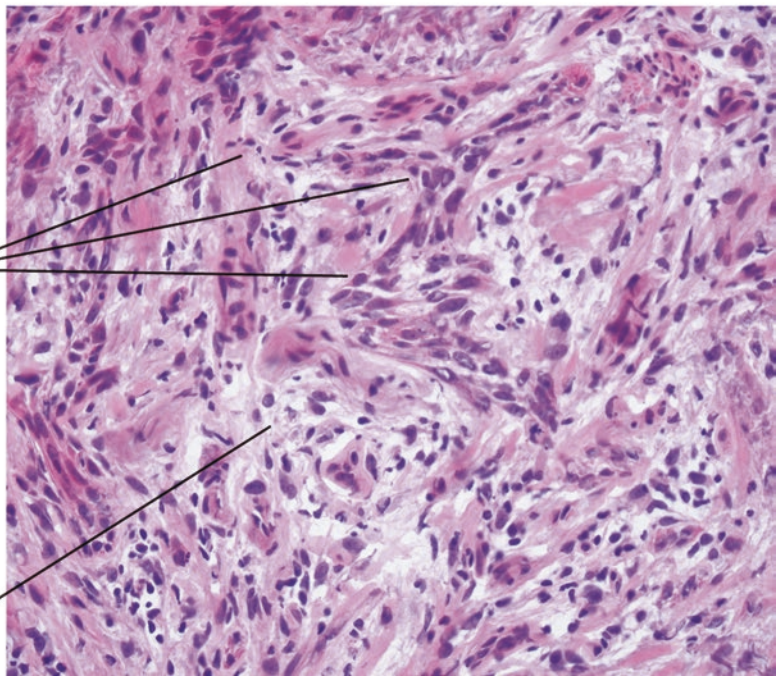
Note: Basilar layer dysplasia and perforating strands of elastin

Variants
Spindle Cell SCC



- Irregular spindle cell proliferation

MEDIUM 6-29

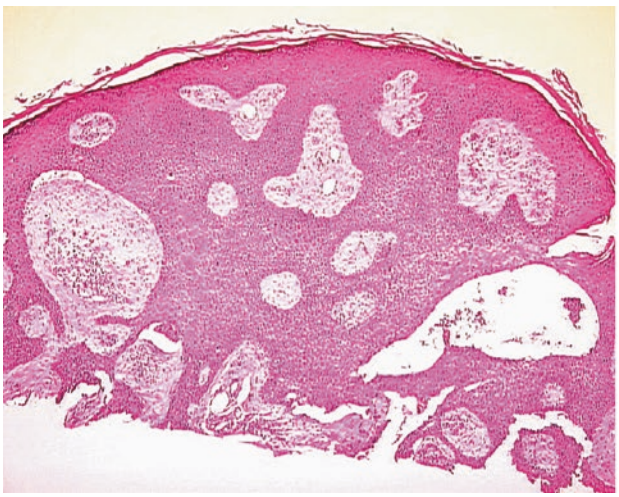


- Spindled cells coalesced to form vague outlined islands

Note: Myxoid and inflamed stroma

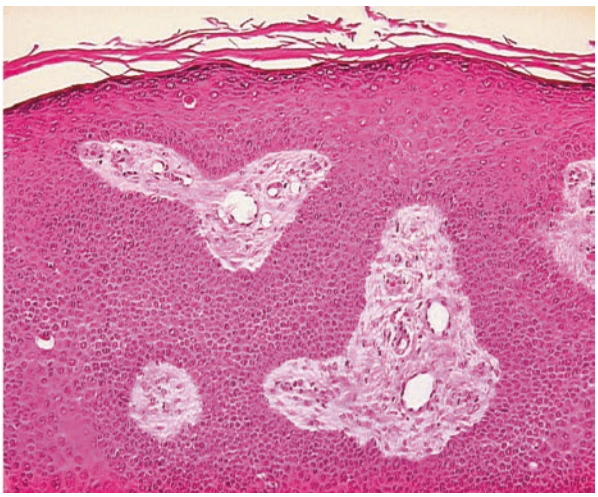
HIGH 6-30

Challenges: SCC Simulant
Poroma



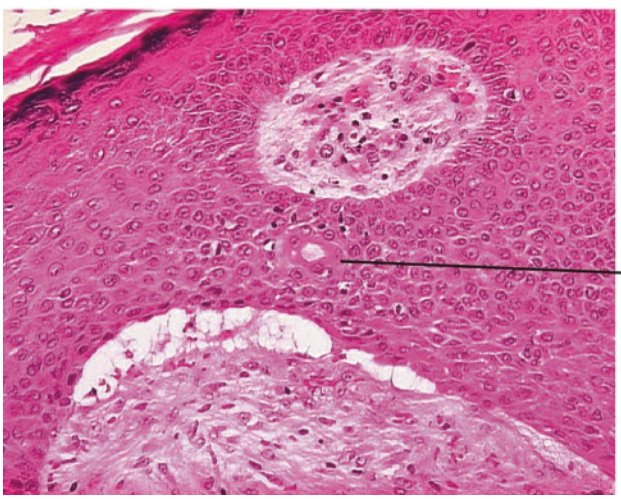
LOW 6-31

- Plate like horizontal arrangement of epithelial cells



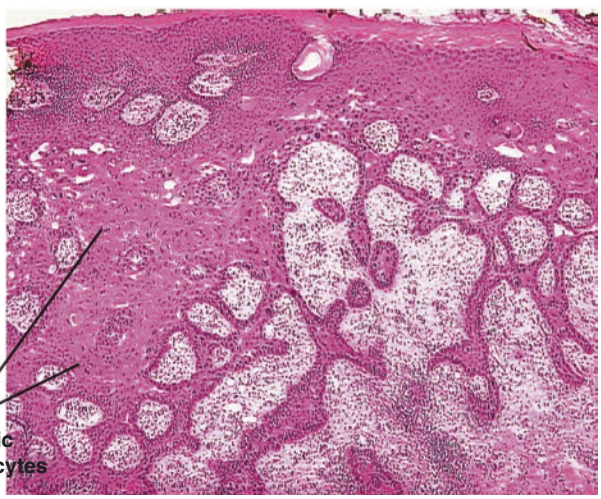
MEDIUM 6-32

- Sheets of uniform epithelial cells with prominent fibrovascular cores



HIGH 6-33

- Intraepithelial pores or ducts

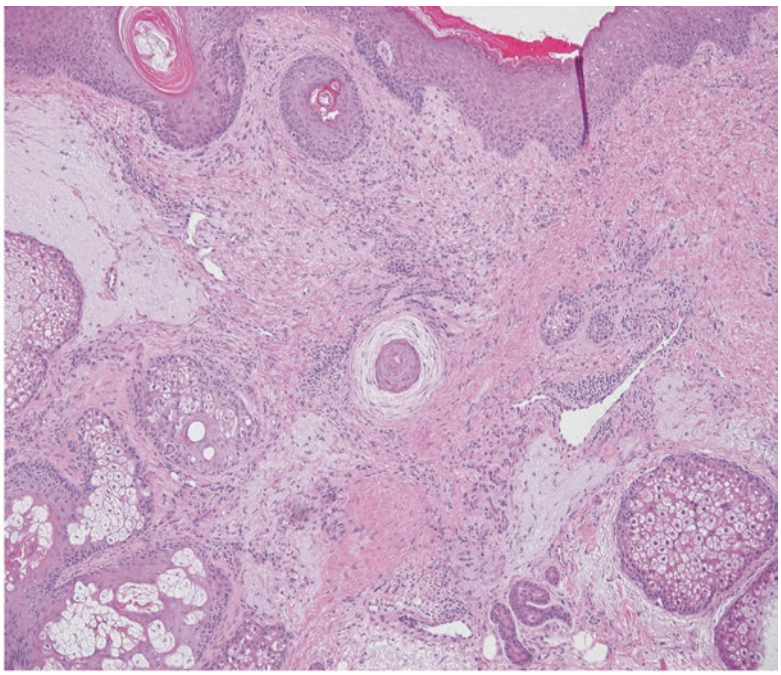


ACRAL SQUAMOUS CELL CARCINOMA 6-34

- Acral SIS often confused with poroma

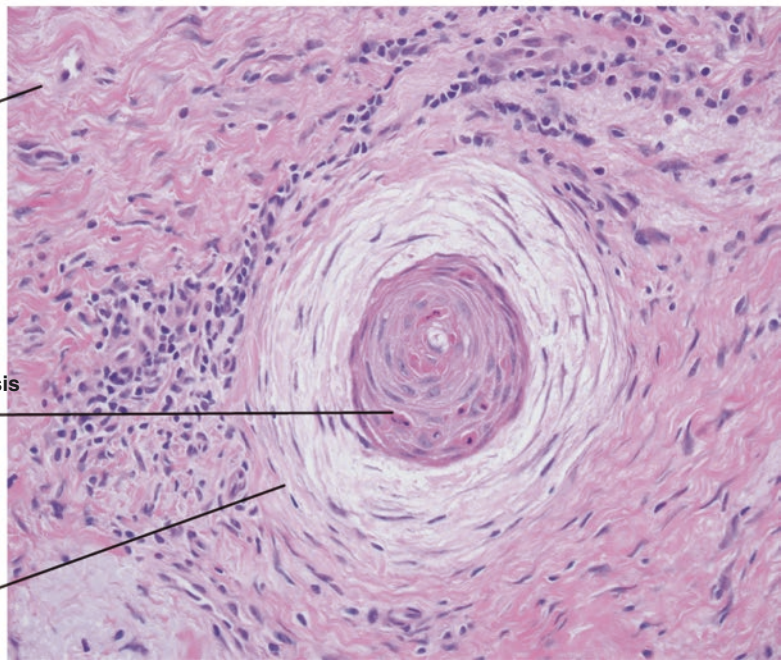
Note: Keratinocyte dysplasia and lack of pores

Challenges: SCC Simulant
Eccrine Syringometaplasia



- Rounded and oval squamous islands seen within scar

MEDIUM 6-35

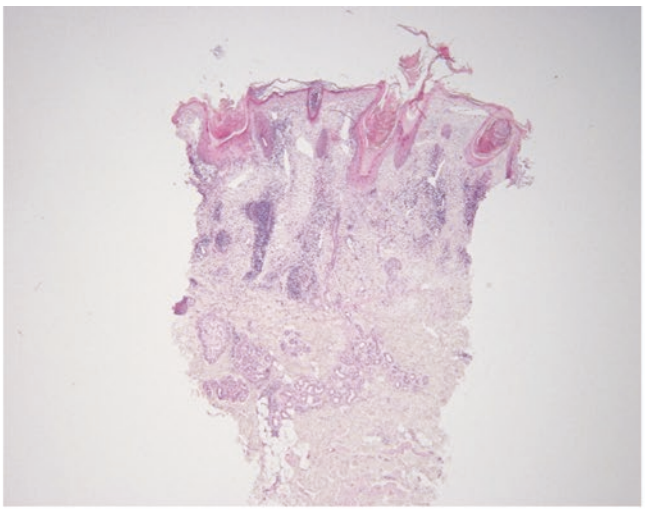


- Rounded silhouette despite dyskeratosis and mitosis

Note: Myxoid mantle

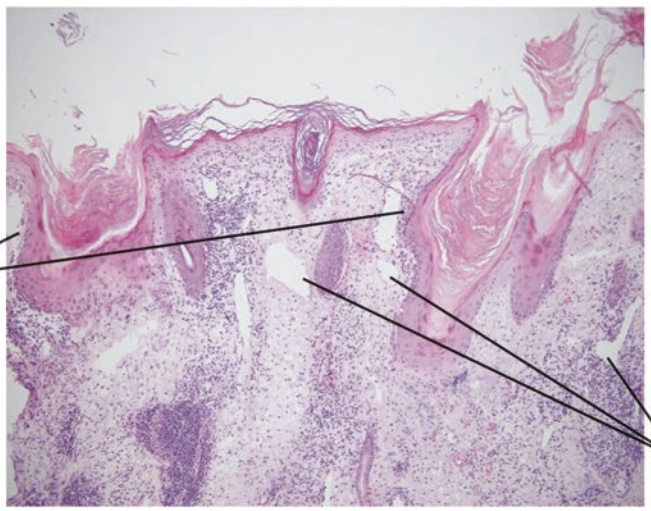
HIGH 6-36

Challenges
Discoid Lupus Erythematosus



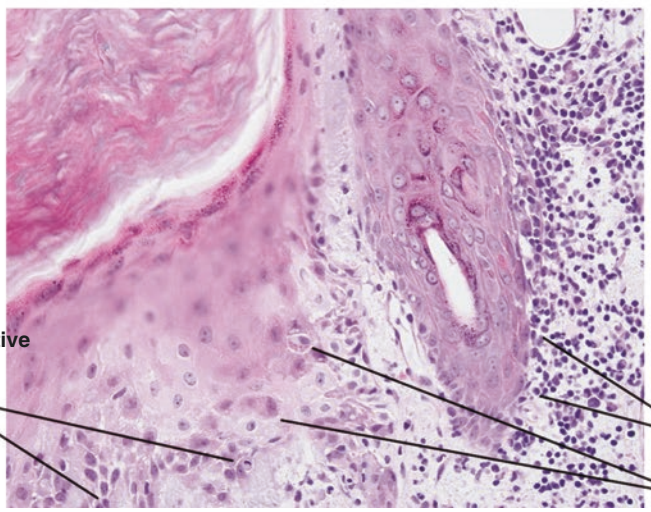
- Variable thickened and thinned epidermis with superficial and deep dermal inflammation

LOW 6-37



- Follicular plugs with capillary ectasia (telangiectasia)

MEDIUM 6-38



- Interface dermatitis
- Ragged basilar epidermis with deskeratosis, dysplasia and pseudo-infiltrative appearance

HIGH 6-39

Bibliography

1. Alam M, Ratner D. Cutaneous squamous cell carcinoma. N Engl J Med. 2001;344:975.
2. Epsteim J. Photocarcinogenesis, skin cancer, and aging. J Am Acad Dermatol. 1983;9:487.
3. Lohmann C, Solomon A. Clinicopathologic variants of cutaneous squamuos cell carcinoma. Adv Anat Pathol. 2001;8:27.

Basal Cell Carcinoma: Variants and Challenges

7

Michael B. Morgan

EPIDEMIOLOGY: 900,000 q Year U.S., incidence increasing 5% q year, Caucasians.
ETIOLOGY: Ultraviolet exposure, irradiation, ulceration, burns, arsenic, coal-tar, genetics.
PATHOGENESIS: PTCH, p53, BAX gene mutations.
CLINICAL:**Nodular**-facial telangectatic papule, **superficial**-scaly truncal patch, **infiltrating/morpheaform**-ill-defined erythematous indurated facial patches.
HISTOLOGY:**Nodular**-large nodules with central necrosis, **superficial**-Multifocal superficial delimited basaloid islands, **pinkus**-retiform extensions of anastomosing basaloid tumor, **keratotic** nodular basaloid tumor with central mature keratinization, **infiltrating-**irregular thick and thin islands of deeply extending basaloid tumor, **morpheaform**-irregular uniformly thinned basaloid tumor coursing throughout dermis, **basosquamous-**composite tumor comprised of malignant squqmous foci with basaloid foci, and **micronodular-**deeply extending uniform small nodules of basaloid tumor.

Basal cell carcinoma (BCC) is the most common cutaneous carcinoma. The annual incidence of BCC in the United States is approximately 1,100,000 cases, which outnumbers the next most prevalent carcinoma (squamous cell carcinoma) by a factor of four and melanoma by a factor of 20. Common to the aforementioned neoplasms, the etiology of BCC is most closely related to excessive ultraviolet exposure and, accordingly, is most commonly diagnosed in the elderly on the exposed cutaneous surfaces, *especially* in *residents* of sunny geographic locales. Exceptions to this rule are rare yet can be observed in certain genetic syndromes that may predispose to multiple BCC's occurring in exceptional anatomic locations and age ranges. These syndromes include xeroderma pigmentosa, the Basex and Basal Cell Nevus syndromes. It is in the latter syndromes that the pathogenesis has been discerned and relates to the development of sporadic forms of this disease as well. The pathogenesis involves mutations in the human homologue of the Drosophila gene *patched* (PTCH1) where it functions as a tumor suppressor gene. Loss of this gene or its function along with acquired (ultraviolet-induced) defects in the p53 gene and the apoptosis-regulating gene BAX has also been implicated in the pathogenesis. Regardless of their underlying cause, these neoplasms may present in a variety of clinical guises depending upon the type or variant disclosed. These variants may be broadly sub categorized on the basis of their respective biologic behaviors as indolent or aggressive. The indolent variants include the most common, nodular type responsible for 75% of cases and typically configured as slow-growing skin-toned papule with surface telangectases located on the face. The next most common indolent variant is the superficial type, typically presenting on the trunk or extremities as a slowly expanding erythematous and scaly patch. A rare variant known as the Pinkus type, typically presents as a slow-growing soft nodule on the trunk or proximal extremities. Finally, there is the keratotic variant, which is considered indolent yet important to histologically distinguish from one of the more aggressive variants known as the basosquamous or metatypical variant. The aggressive variants include infiltrating, morpheaform,

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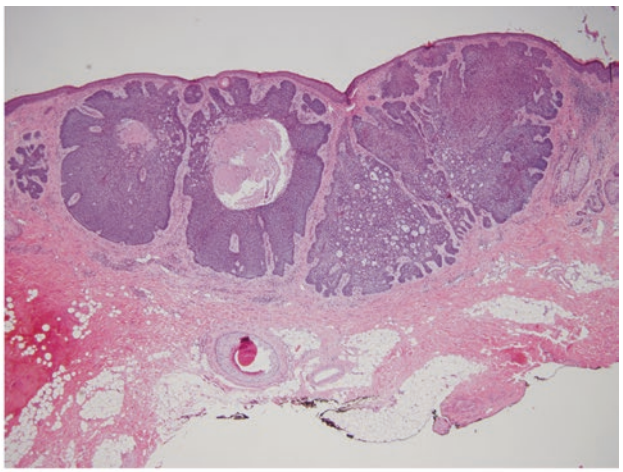
https://doi.org/10.1007/978-3-319-74847-4_7

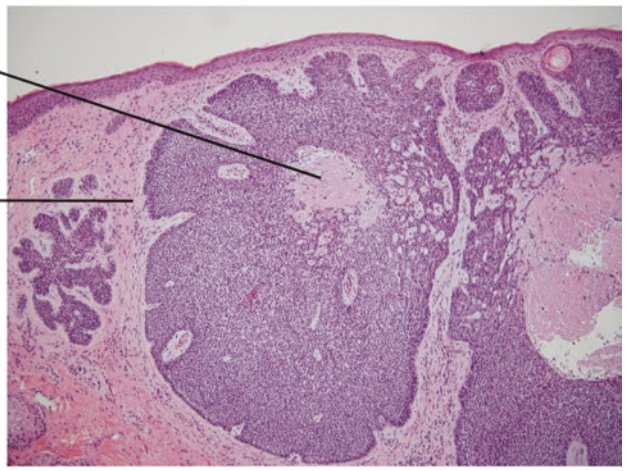
basosquamous and micronodular types. The infiltrating and morpheaform types similarly present as more rapidly expanding ill-defined erythematous indurated patches located on the face. The basosquamous variant typically presents as a rapidly growing often hyperkeratotic and ulcerated nodule on the face. The micronodular variant is capable of presenting in a variety of guises including non-descript truncal or extremity papules.

Indolent - BCC Variants
Nodular



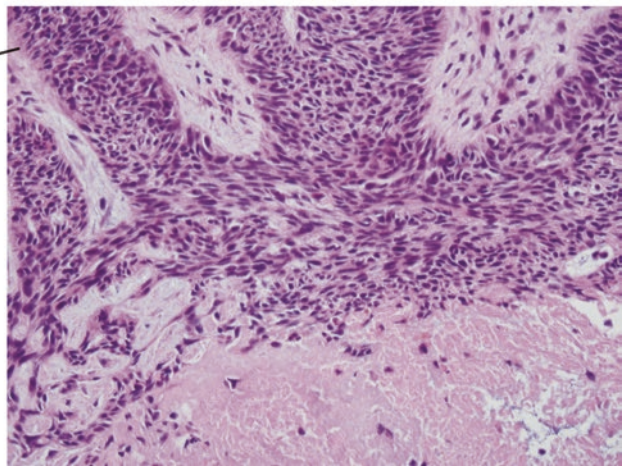
NODULAR *LOW* 7-1

- Asymmetric horizontal disposed basaloid neoplasm
- Often multifocal
- Connection with overlying epithelium



NODULAR *MEDIUM* 7-2

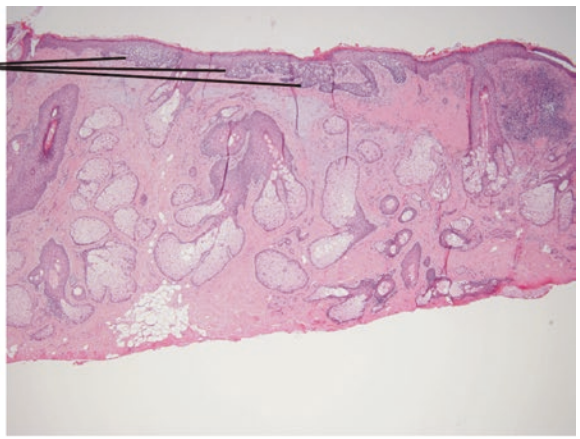
- Larger nodules show central necrosis
- Investing myxoid stroma



NODULAR *HIGH* 7-3

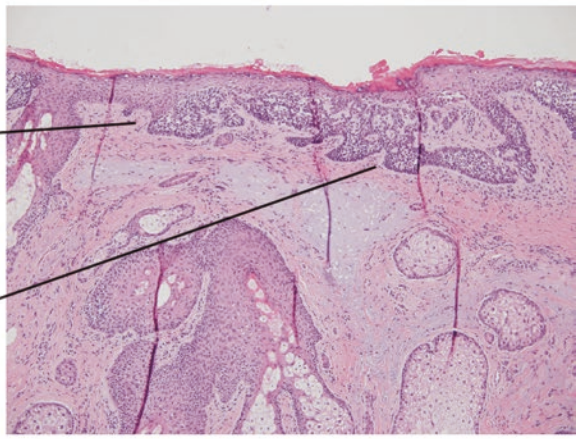
- Peripheral palisading
- Uniform population of hyperchromatic basaloid cells

Indolent - BCC Variants
Superficial



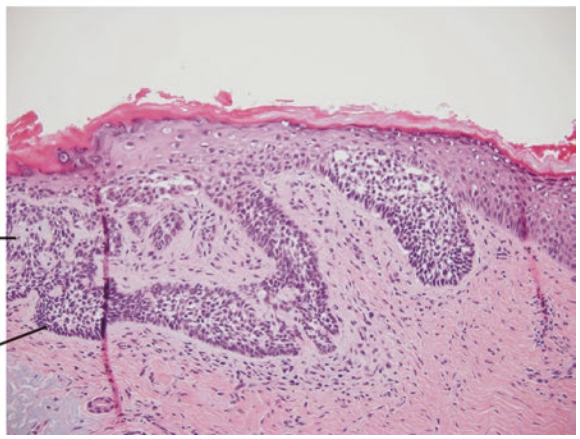
SUPERFICIAL *LOW* 7-4

- Multifocal horizontal disposed basaloid neoplasm
- Intimate connection/association with epithelium



SUPERFICIAL *MEDIUM* 7-5

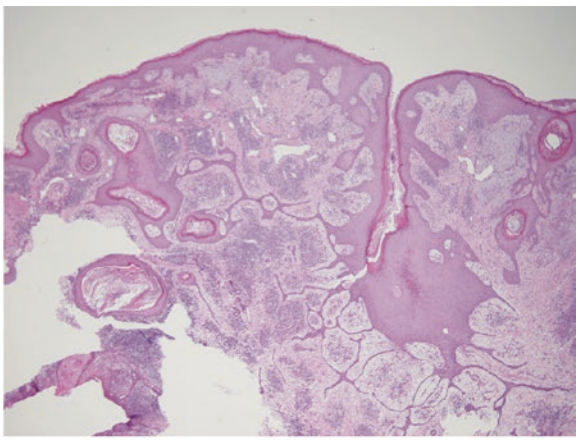
- Bulbous basaloid extensions
- Anastomosing basaloid foci



SUPERFICIAL *HIGH* 7-6

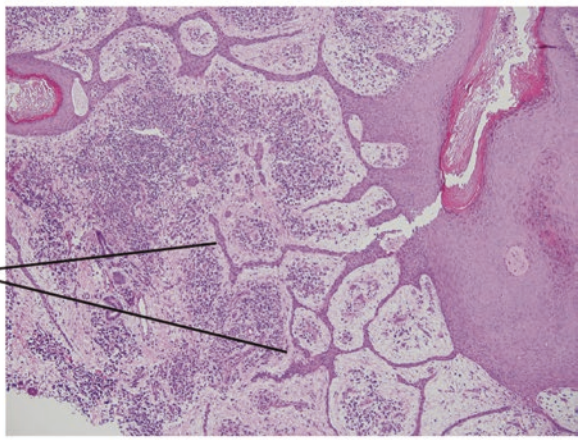
- Peripheral Palisading
- Uniform population of basaloid cells
- Myxoid Stroma

Indolent - BCC Variants
Pinkus Tumor



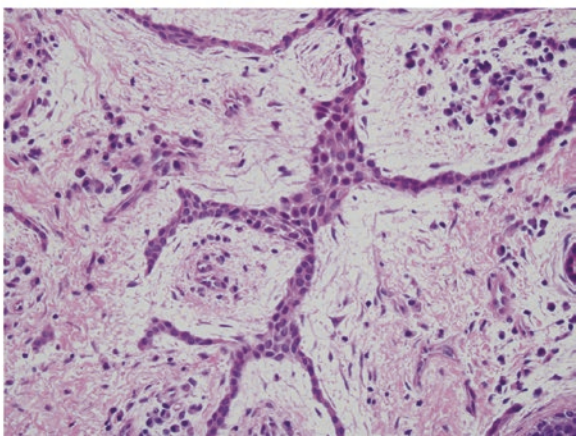
PINKUS *LOW* 7-7

- Horizontal and vertically orientated basaloid neoplasm



PINKUS *MEDIUM* 7-8

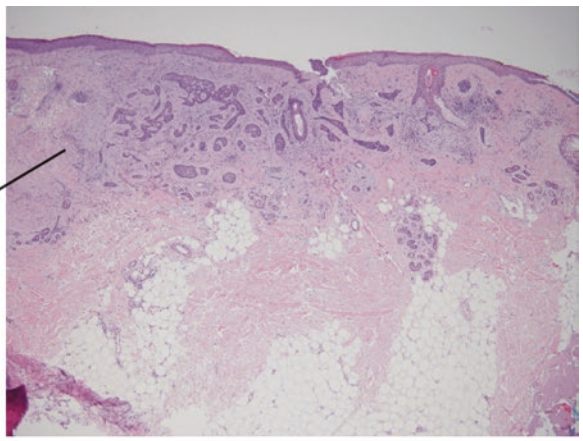
- Anastomosing retiform extensions of tumor



PINKUS *HIGH* 7-9

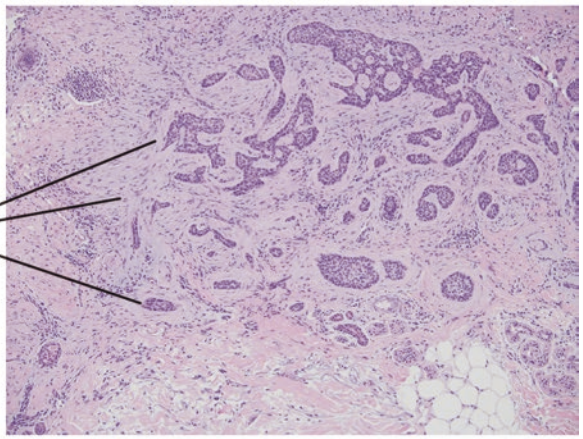
- Anastomosing retiform tumor foci
- Myxoid stroma containing chronic inflammatory cells

Aggressive - BCC Variants
Infiltrating



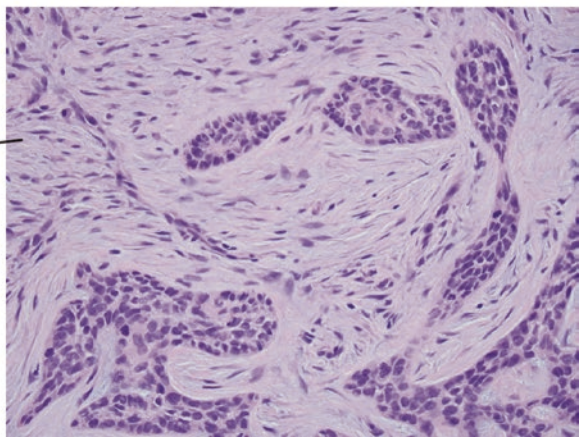
INFILTRATING *LOW* 7-10

- Irregular vertical and horizontal arrangement with stranding of basaloid tumor



INFILTRATING *MEDIUM* 7-11

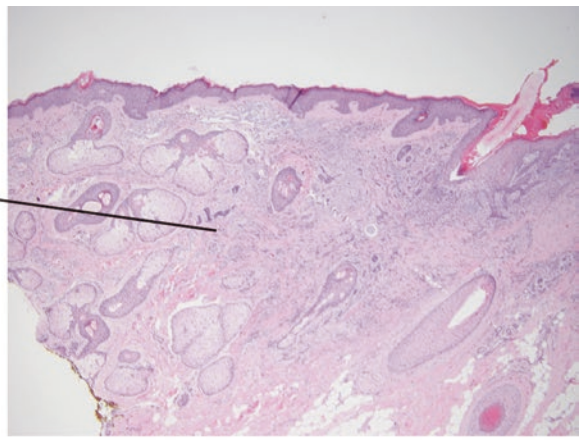
- Jagged outlined basaloid tumor
- Heterogeneous shapes/orientation



INFILTRATING *HIGH* 7-12

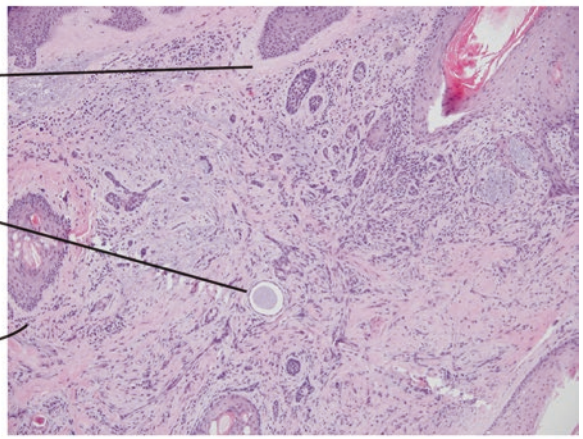
- Abundant grey cellular "desmoplastic" stroma
- Thin, oval and irregular outlined tumoral foci

Aggressive - BCC Variants
Morpheaform



MORPHEAFORM *LOW* 7-13

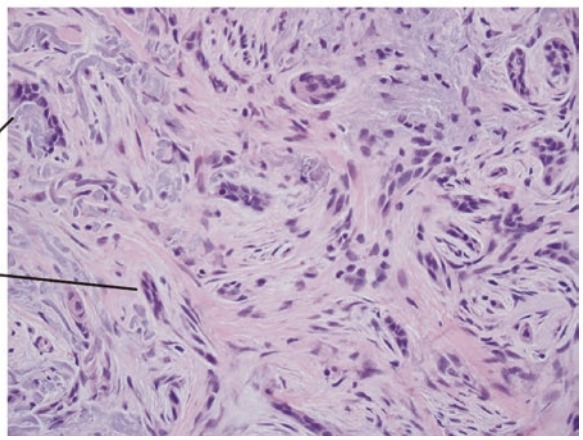
- Subtle-vertical oriented basaloid neoplasm



MORPHEAFORM *MEDIUM* 7-14

- Irregular outlined thin basaloid strands
- Extension around native adnexal structures

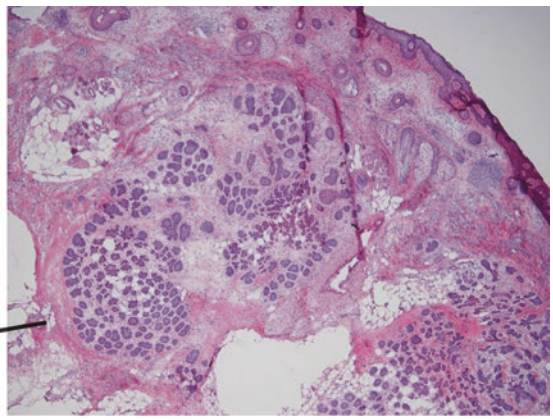
Note: Not uncommon to see grenz zone



MORPHEAFORM *HIGH* 7-15

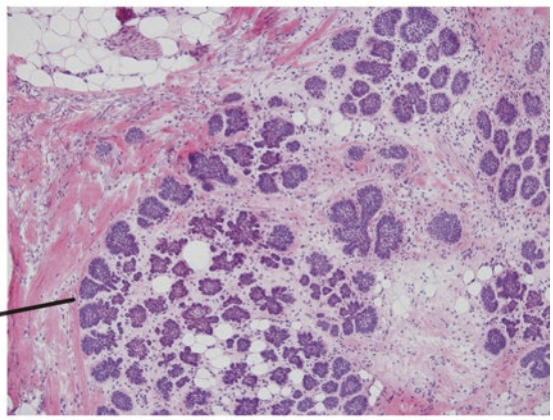
- " Taffy-Pull" like thinned basaloid strands typically less than 3 cell layers thick
- Abundant desmoplastic stroma (this is the most important dichotomy with infiltrating BCC)

Aggressive - BCC Variants
Micronodular



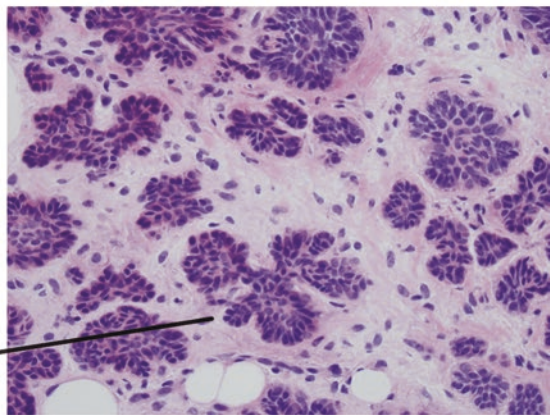
MICRONODULAR *LOW* 7-16

- Deeply extending, vertically-oriented basaloid neoplasm



MICRONODULAR *MEDIUM* 7-17

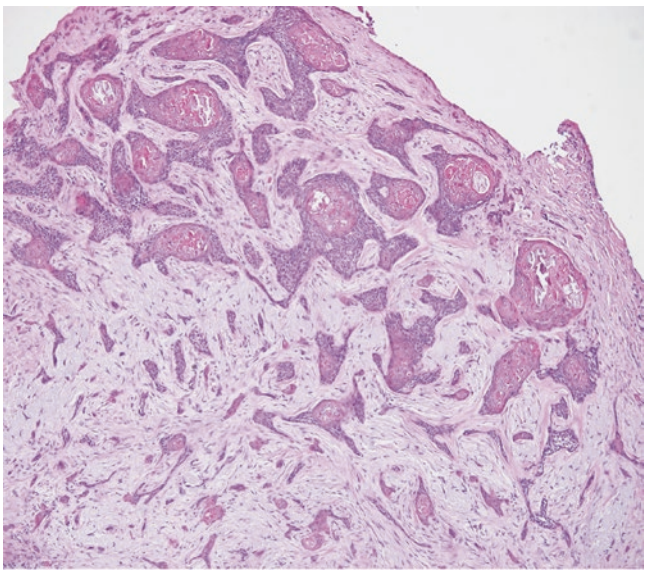
- Multifocal small uniform micronodules of basaloid tumor



MICRONODULAR *HIGH* 7-18

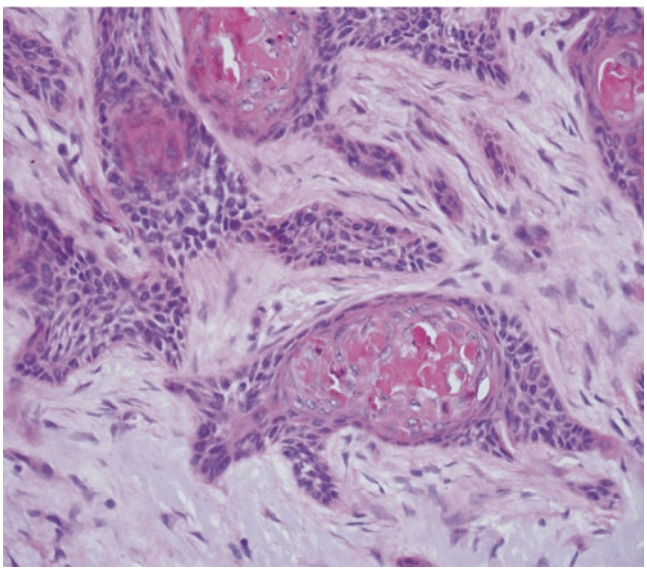
- "Benign" appearing floret-like basaloid islands

Aggressive - BCC Variants
Basosquamous Carcinoma



BASOSQUAMOUS CARCINOMA *MEDIUM* 7-19

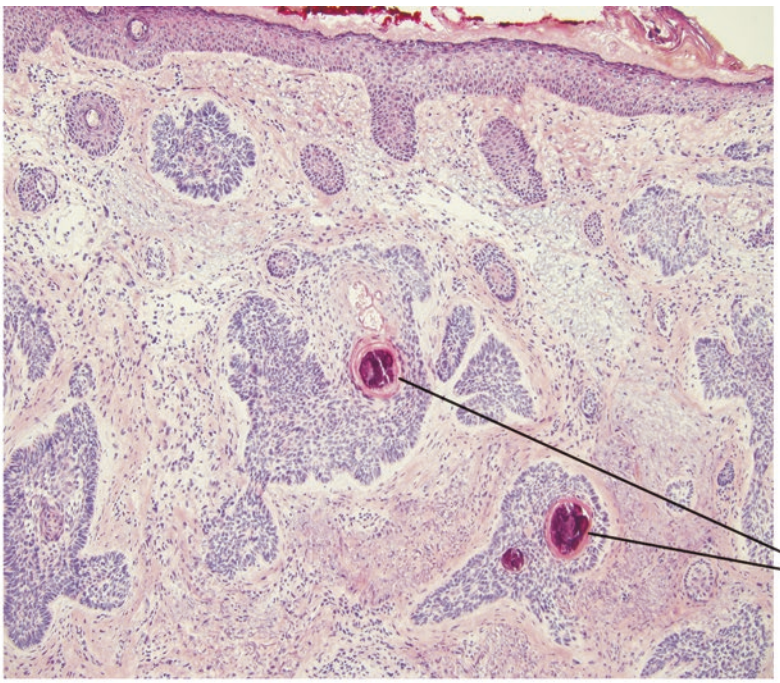
- Jagged and irregular biphasic tumor



BASOSQUAMOUS CARCINOMA *HIGH* 7-20

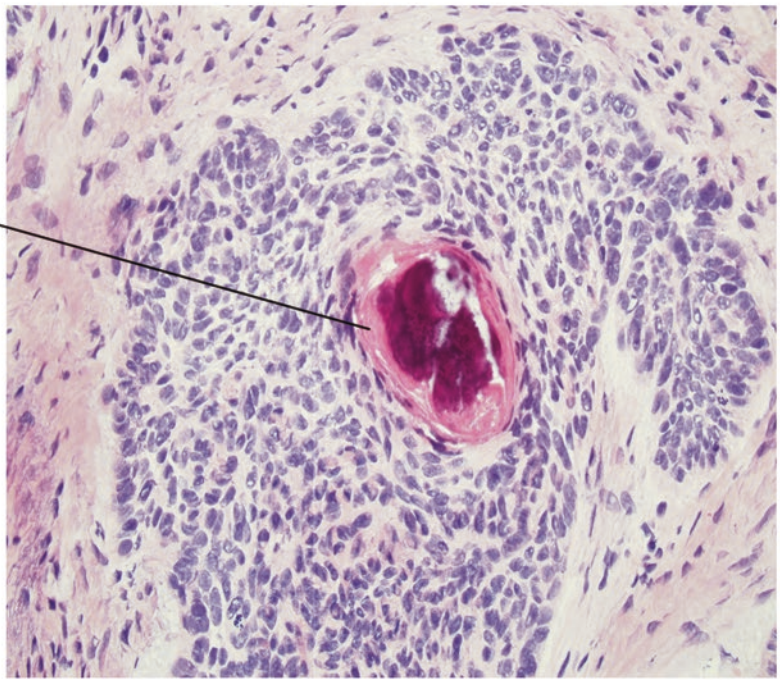
- Biphasic tumor comprised of malignant peripheral palisading basaloid and central malignant squamous epithelium

Indolent - BCC Variants
Keratinizing



- Rounded basaloid foci with central keratinization

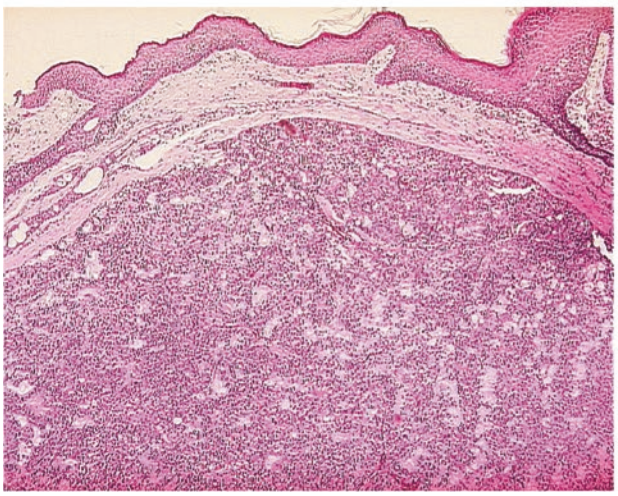
KERATINIZING BCC *MEDIUM* 7-21



Note: Central mature keratinization

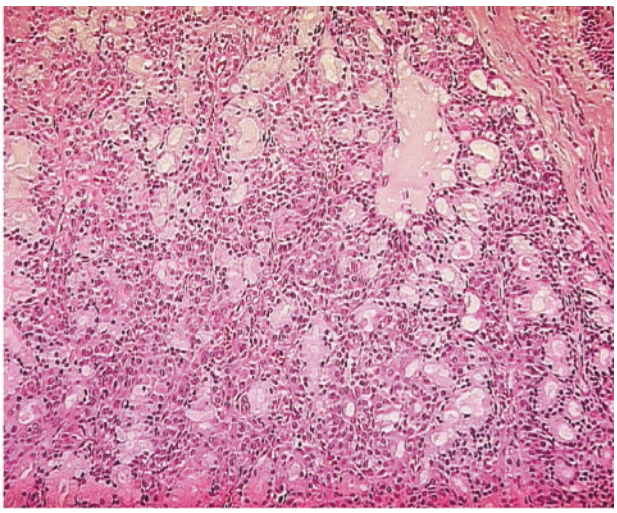
KERATINIZING BCC *HIGH* 7-22

Challenges: BCC Simulant
Hidrandenoma



LOW 7-23

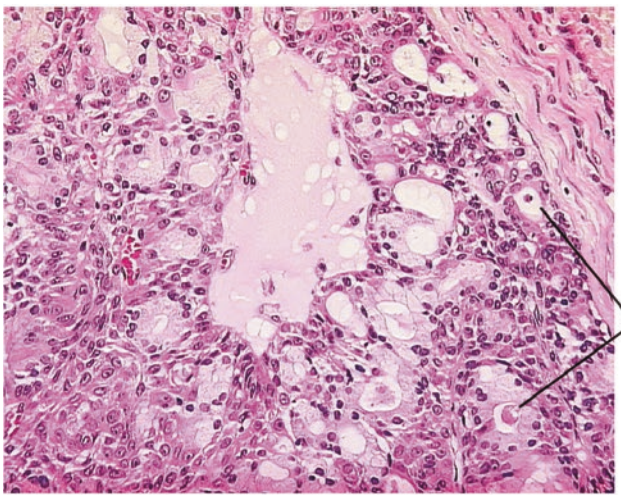
- Well circumscribed collection of dermal glands



MEDIUM 7-24

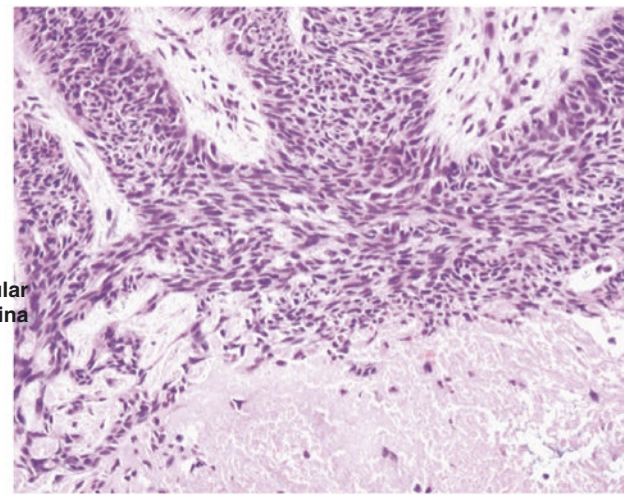
- Glandular and solid cellular foci

Note: Lack of peripheral palisading



HIGH 7-25

- Detail of glandular foci

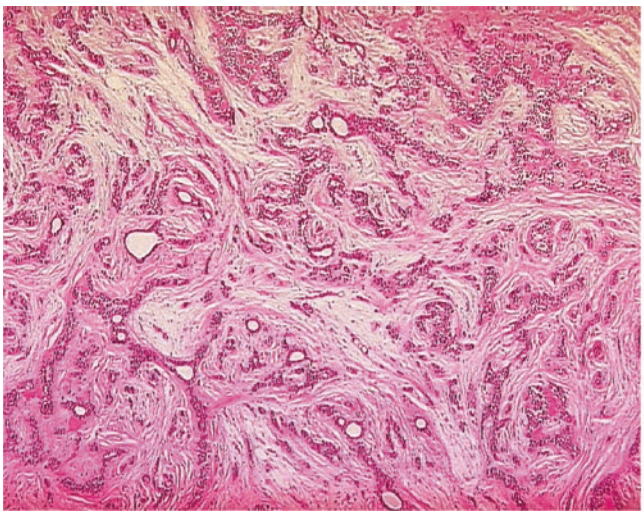


NODULAR BCC *HIGH* 7-26

- Basaloid neoplasm

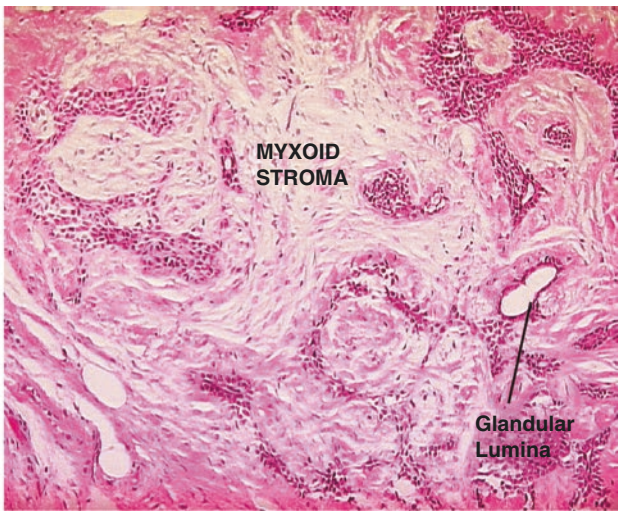
Note: Peripheral palisading

Challenges: BCC Simulant
Benign Mixed Tumor



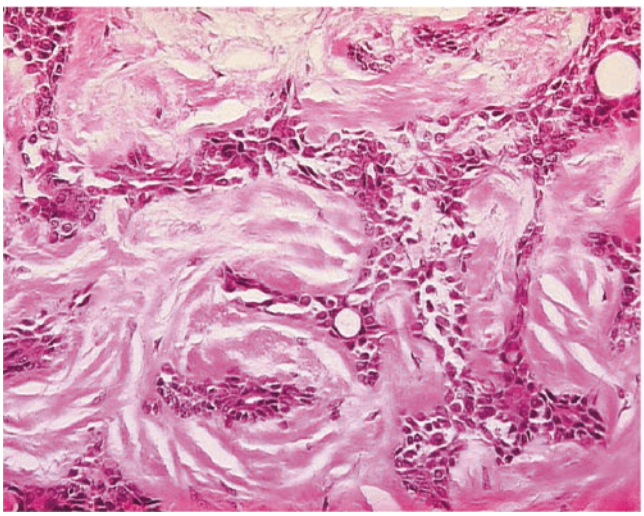
LOW 7-27

- Biphasic proliferation of glands and stroma



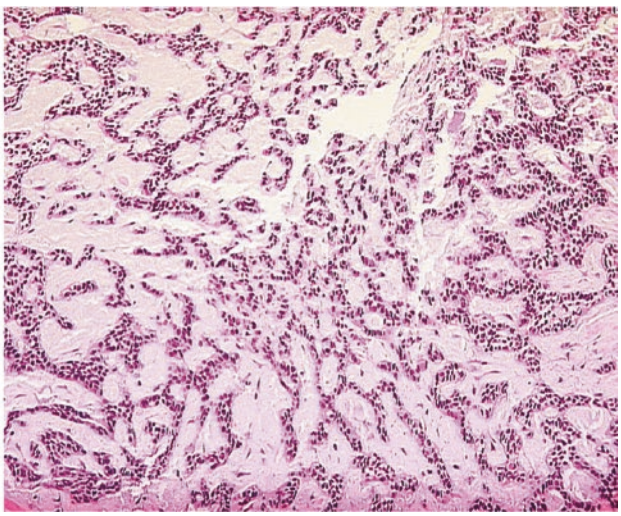
MEDIUM 7-28

Note; Glandular lumina and myxoid stroma



HIGH 7-29

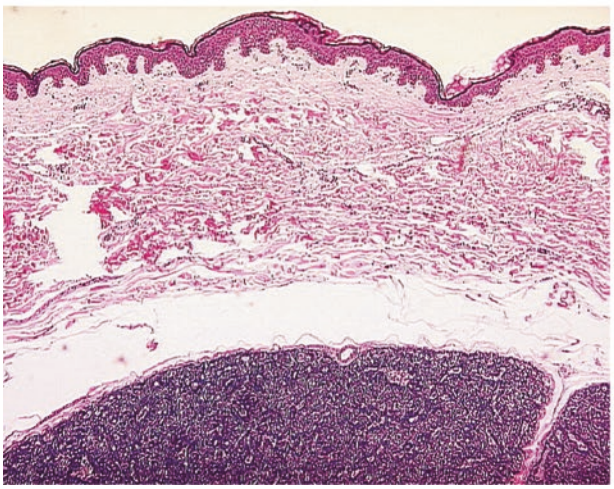
- Detail of glandular arrangement



MYXOID BCC 7-30

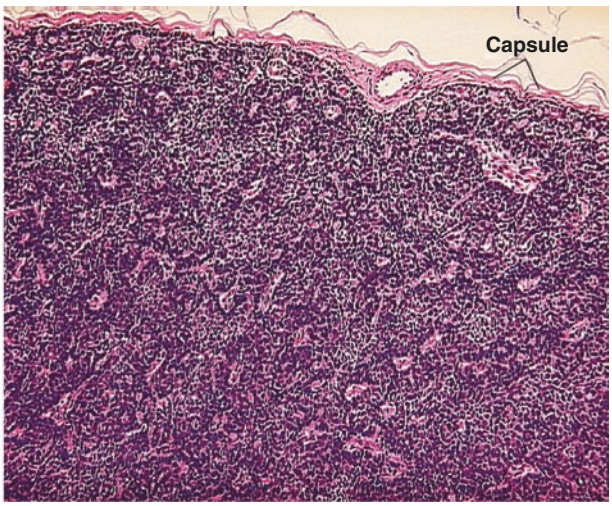
- More dispersed basaloid epithelial cells with diffuse myxoid background

Challenges: BCC Simulant
Spiradenoma



LOW 7-31

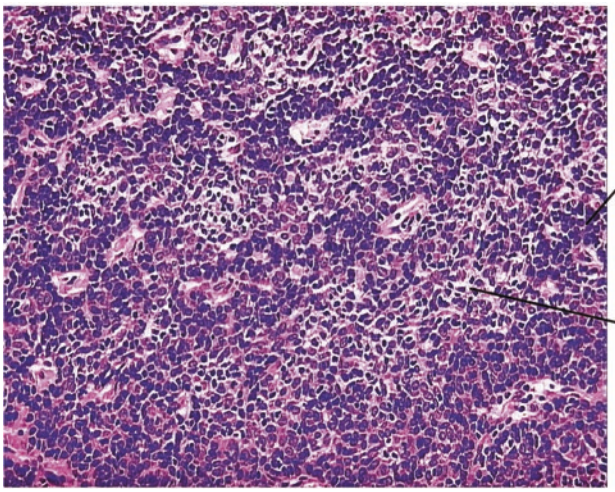
- Deep dermal unifocal well-circumscribed tumor



MEDIUM 7-32

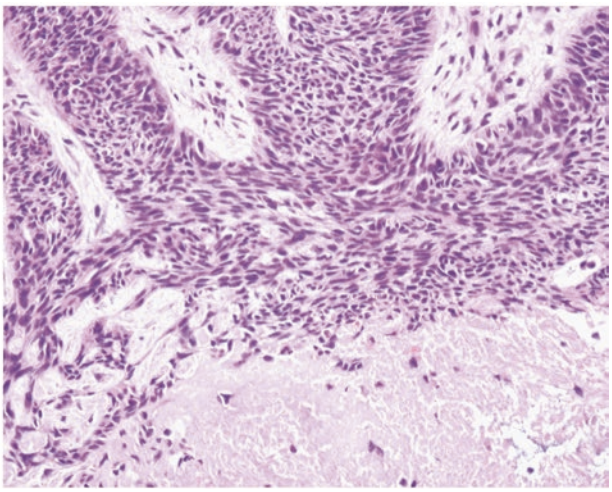
- Heterogeneous basaloid cells

Note: Absence of palisading and thin capsule



HIGH 7-33

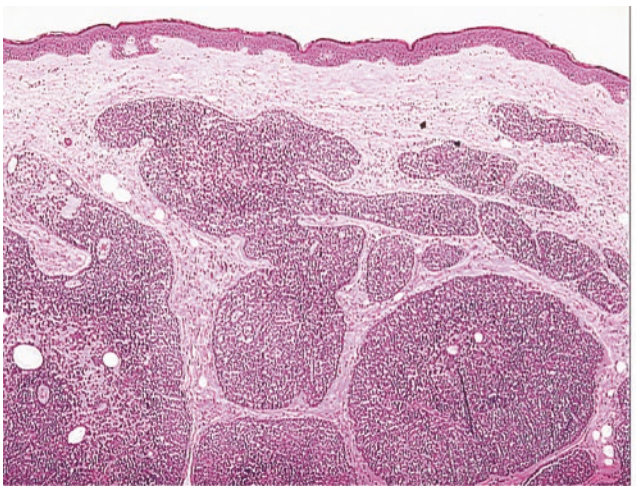
- Detail of biphasic (light and dark) cellular composition



NODULAR BCC *HIGH* 7-34

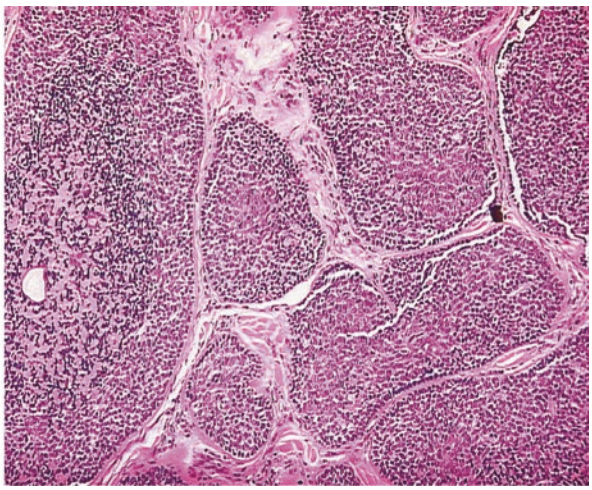
- Basaloid tumor with peripheral palisading

Challenges: BCC Simulant
Cylindroma



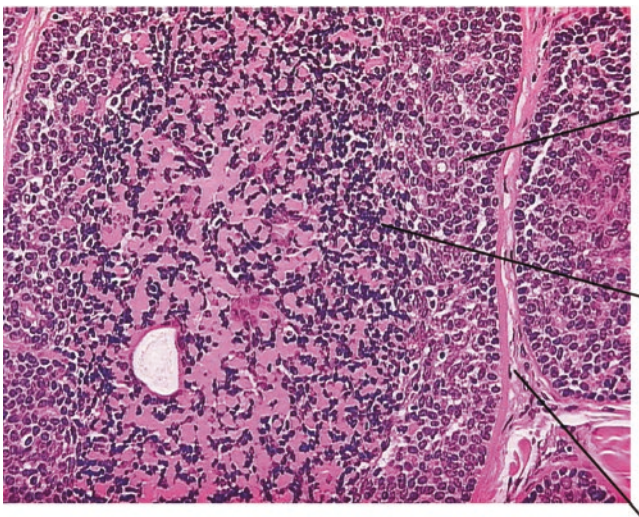
LOW 7-35

- Multifocal deep dermal basaloid neoplasm



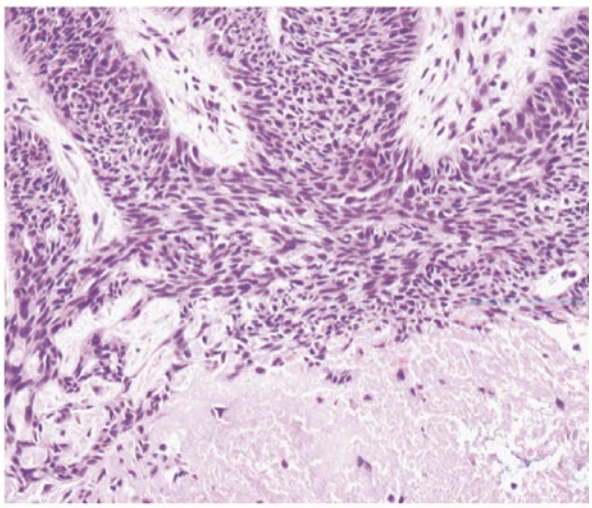
MEDIUM 7-36

- Close apposition of tumoral foci likened to jigsaw puzzle



HIGH 7-37

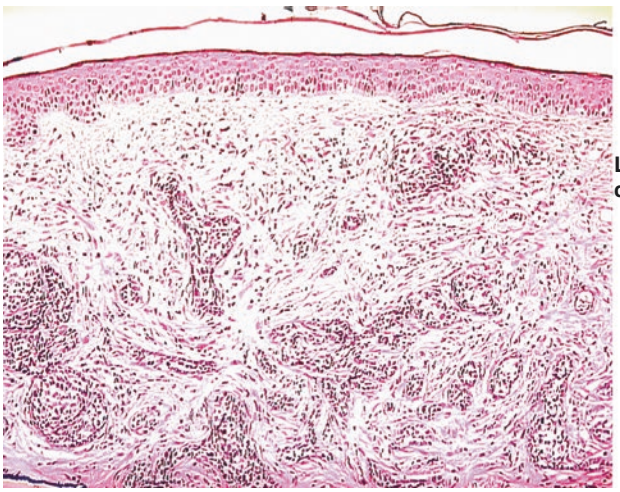
Note: Biphasic cellular constituency
Note: Prominent basement membrane



NODULAR BCC *HIGH* 7-38

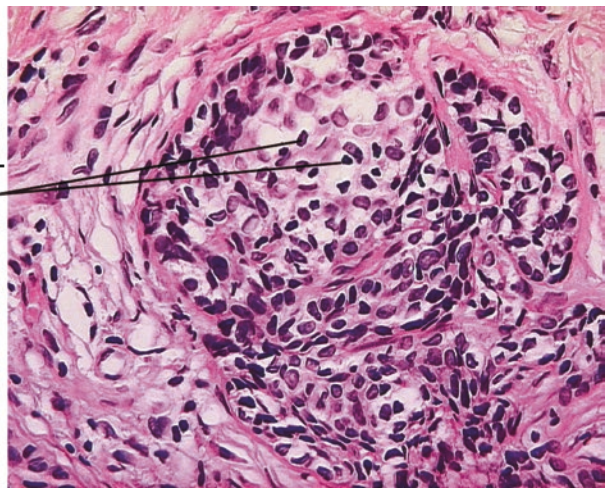
- Uniform basaloid tumor with peripheral palisading, no basement membrane

Challenges: BCC Simulant
Benign Cutaneous Lymphadenoma



LOW 7-39

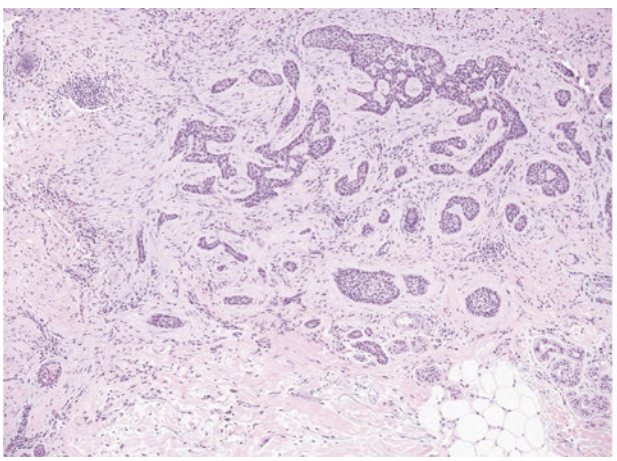
- Irregular basaloid tumoral islands containing lymphocytes



MEDIUM 7-40

- Detail of neoplasm

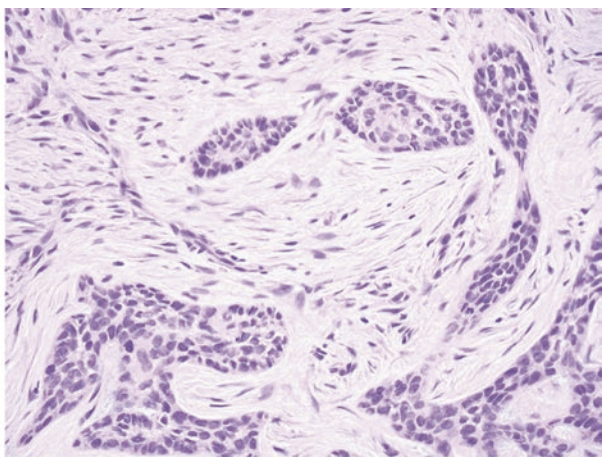
Note: Characteristic infiltration of lymphocytes and absence of clefting and palisading



INFILTRATING BCC *MEDIUM* 7-41

- Irregular infiltrative basaloid tumor

Note: Desmoplastic stroma

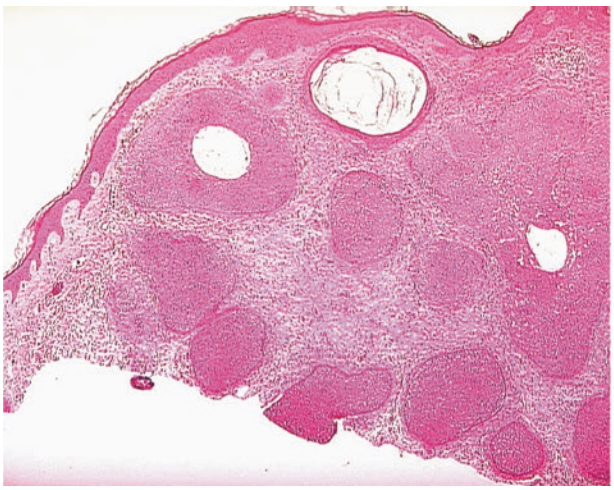


INFILTRATING BCC *HIGH* 7-42

- Detail of basaloid foci

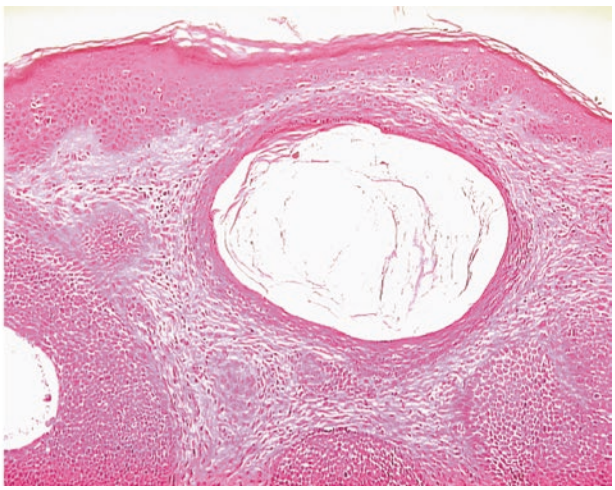
Note: Absence of lymphocytes

Challenges: BCC Simulant
Large Nodular Trichoblastoma



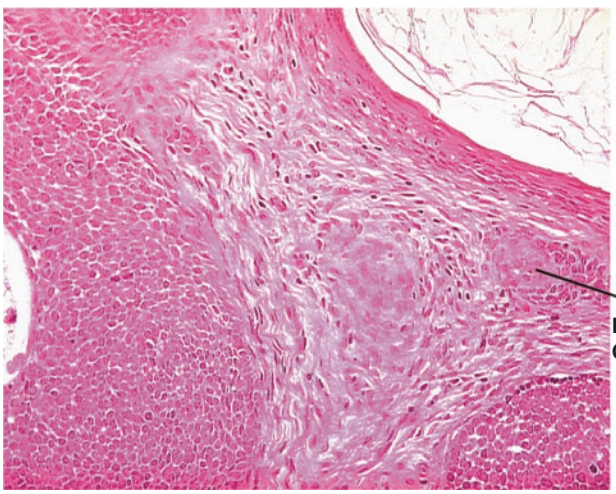
LOW 7-43

- Infiltrating large nodular basaloid foci



MEDIUM 7-44

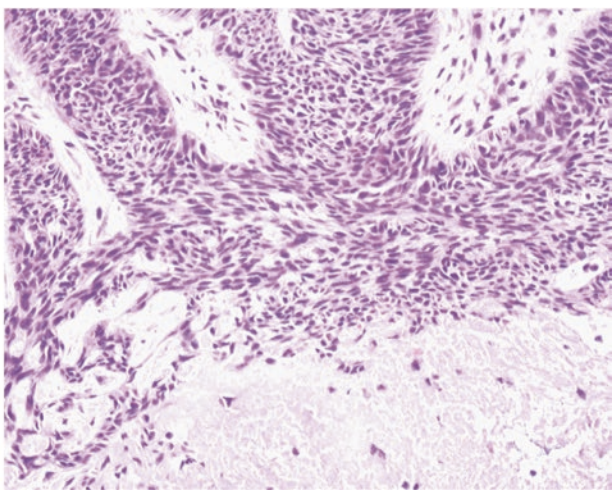
Note: The presence of cysts and cellular stroma



HIGH 7-45

- Detail of basaloid foci

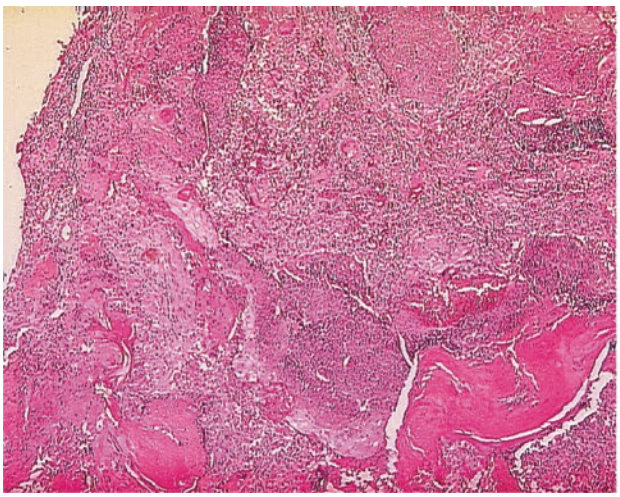
Note: Absence of palisading/clefting and the presence of follicular germs



NODULAR BCC *HIGH* 7-46

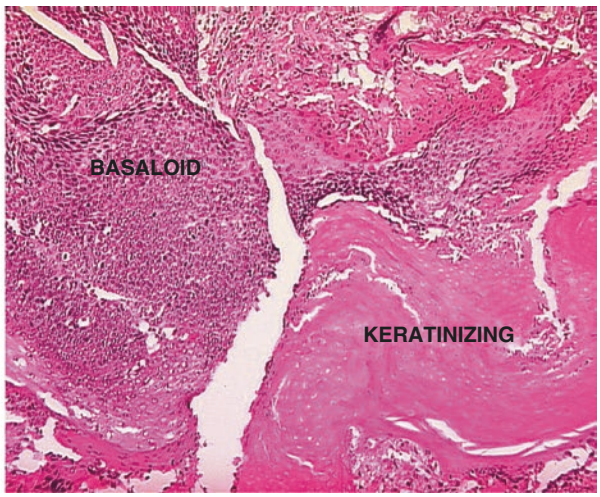
- Basaloid neoplasm without follicular differentiation

Challenges: BCC Simulant
Pilomatricoma



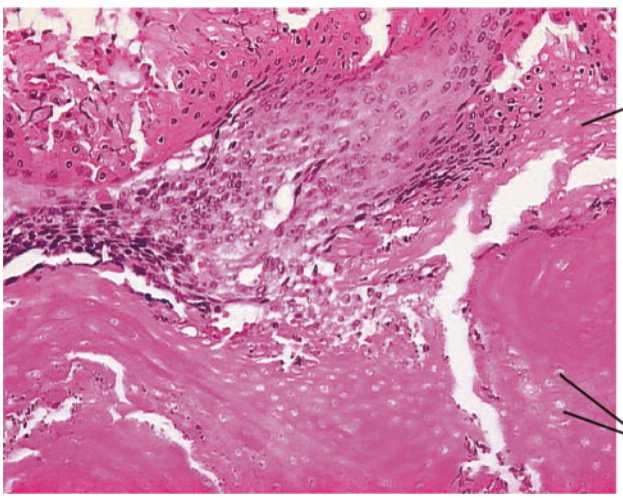
LOW 7-47

- Biphasic neoplasm



MEDIUM 7-48

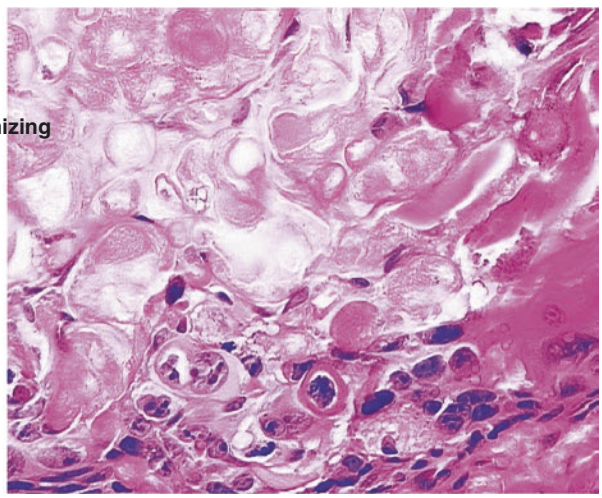
- Detail of basaloid and keratinized foci



HIGH 7-49

- Detail of matricial differentiation

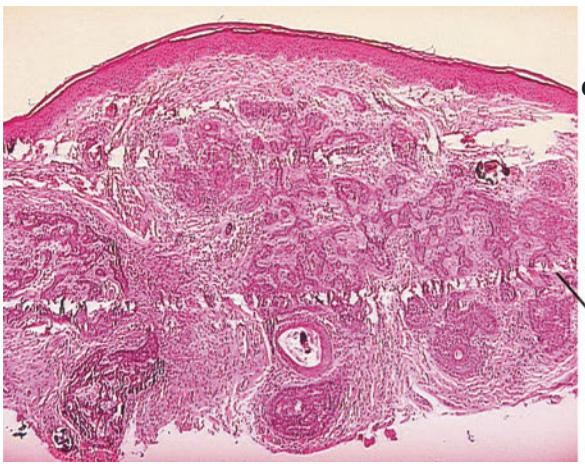
Note: Ghost cells and abrupt keratinization



MATRICIAL CARCINOMA 7-50

- Detail of matricial differentiation with malignant keratinizing cells

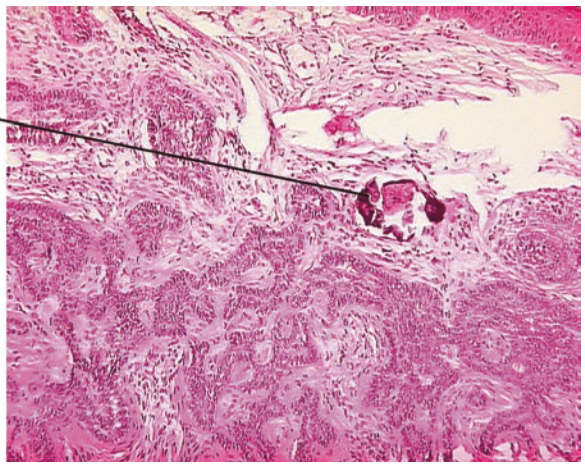
Challenges: BCC Simulant
Trichoepithelioma



LOW 7-51

- Complex basaloid tumor with abundant stroma

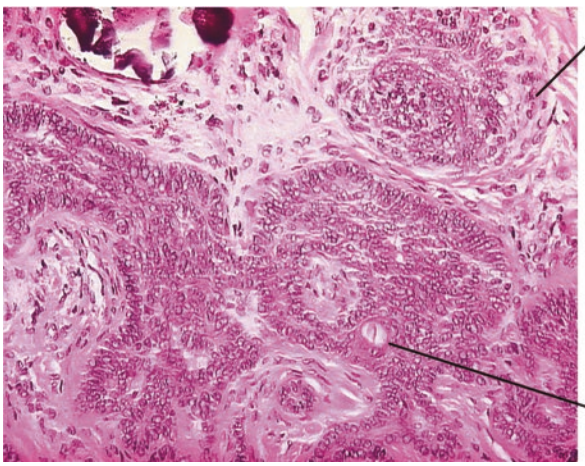
Note: Horizontal streak artifact produced by retained calcification



MEDIUM 7-52

- Complex fenestrated array of basaloid foci

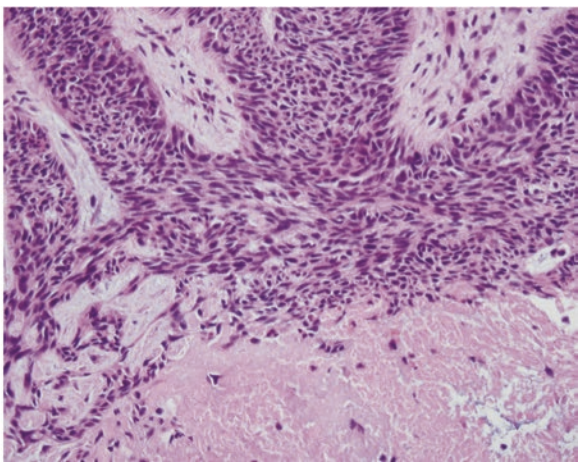
Note: Calcification (uncommon in BCC)



LOW 7-53

- Detail of basaloid foci

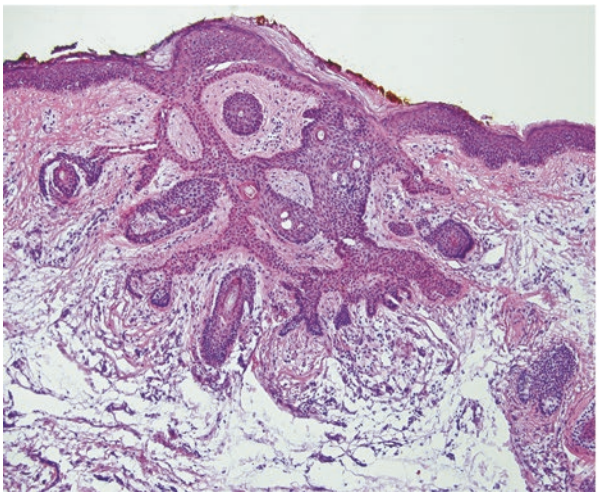
Note: Ductules and follicular germs



NODULAR BCC *HIGH* 7-54

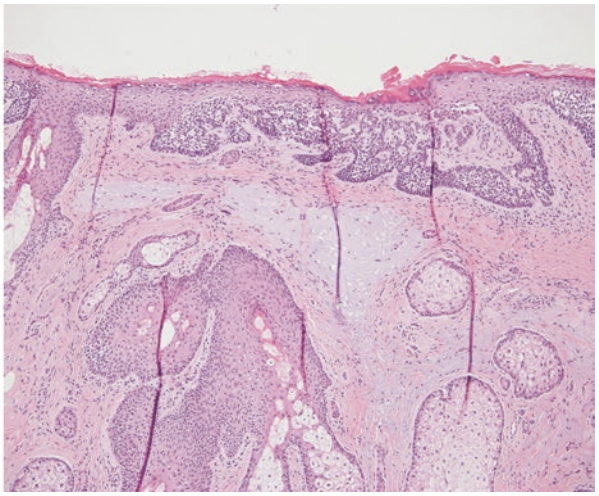
- Uniform population of basaloid cells without ductules or follicular germs

Challenges
Tumor of the Follicular Infundibulum (TFI) vs. Superficial BCC



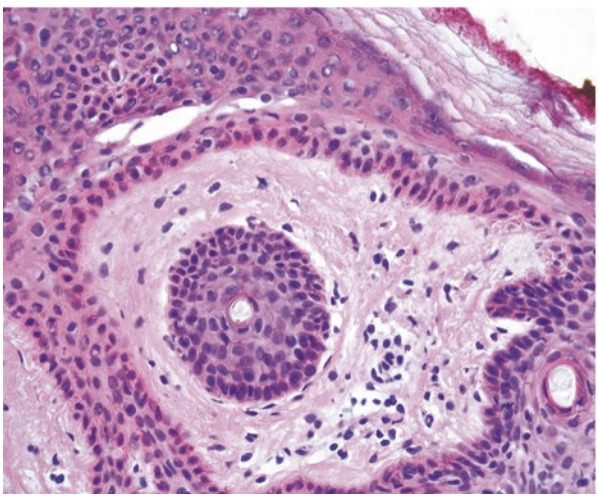
TFI 7-55

- Complex interwoven arrangement
- Discrete, focal



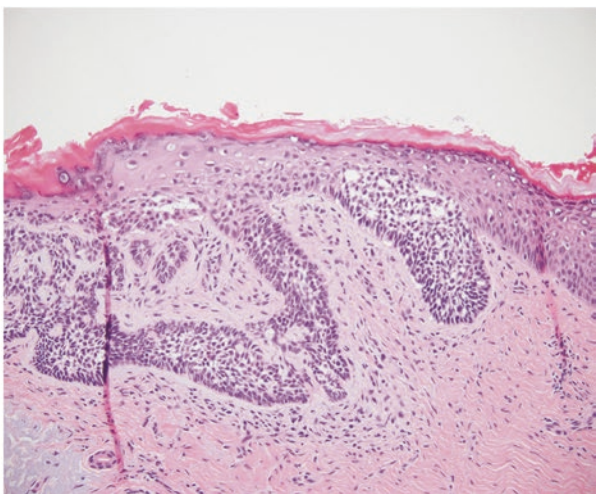
SUPERFICIAL BCC 7-56

- Rudimentary Anastomoses
- Multifocal



TFI 7-57

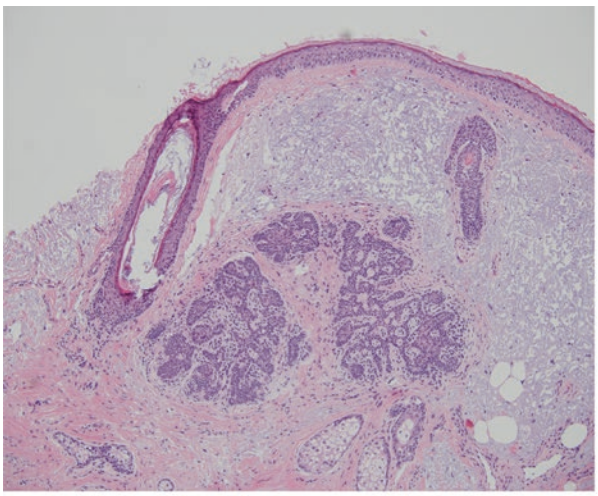
- No Myxoid Stroma
- Vague Palisading
- Pink Cytoplasm



SUPERFICIAL BCC 7-58

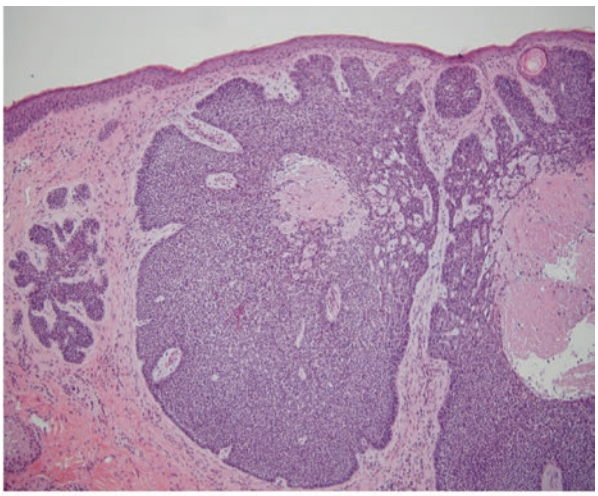
- Myxoid Stroma
- Palisading
- Basaloid Tumor Cells

Challenges
Trichoblastoma vs. Nodular



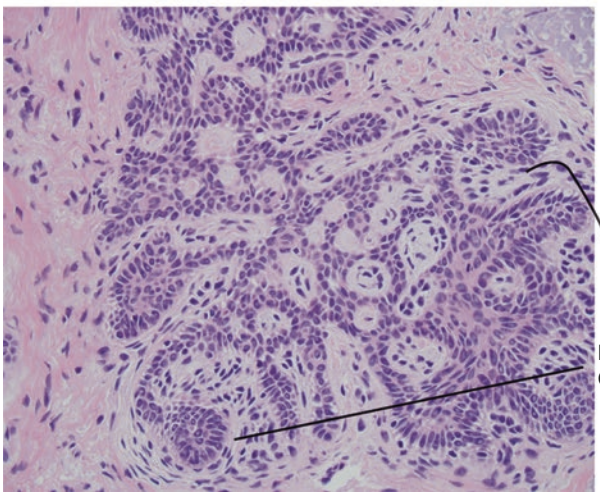
TRICHOBLASTOMA *MEDIUM* 7-59

- No connection/association with epithelium
- Rounded, sysmmetrical silhouette



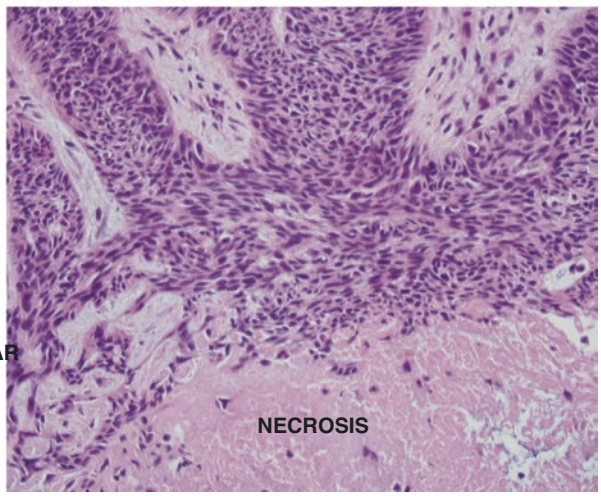
NODULAR *MEDIUM* 7-60

- Connection/association with epithelium
- Asymmetrical silhouette



TRICHOBLASTOMA *HIGH* 7-61

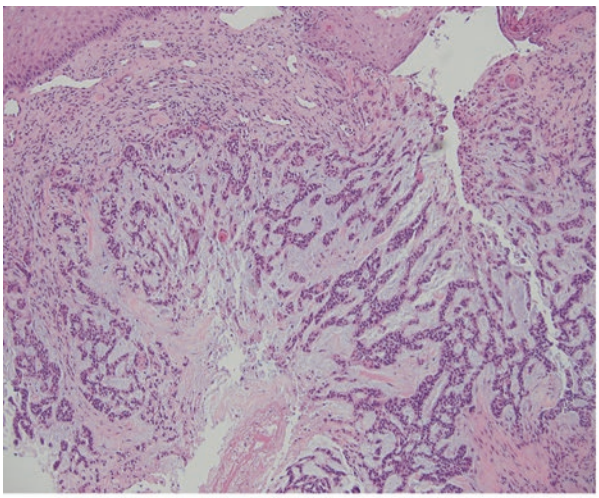
- Follicular germs recapitulating follicles



NODULAR *HIGH* 7-62

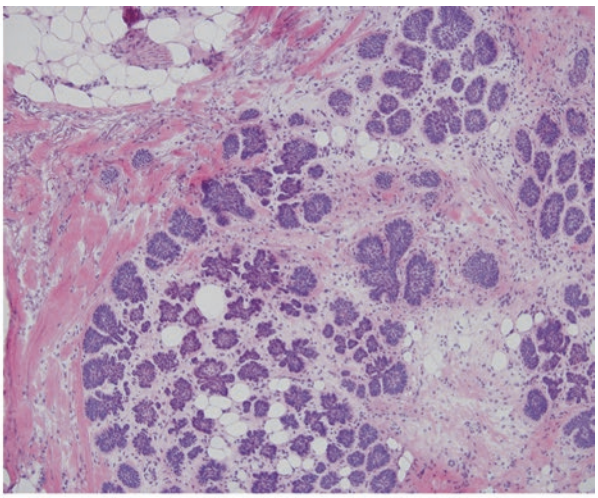
- Primordial basaloid tumor
- Increased mitosis and necrosis

Challenges
Myxoid vs. Micronodular



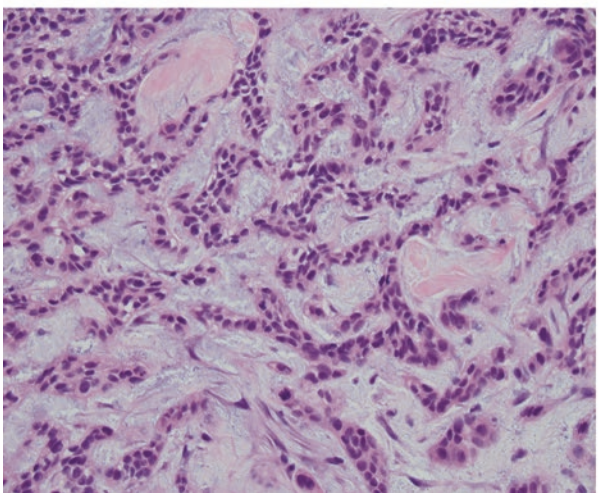
MYXOID *MEDIUM* 7-63

- Vaguely noduluar aggregate arrangement
- Abundant grey mucoid stroma
- Superficial dermis



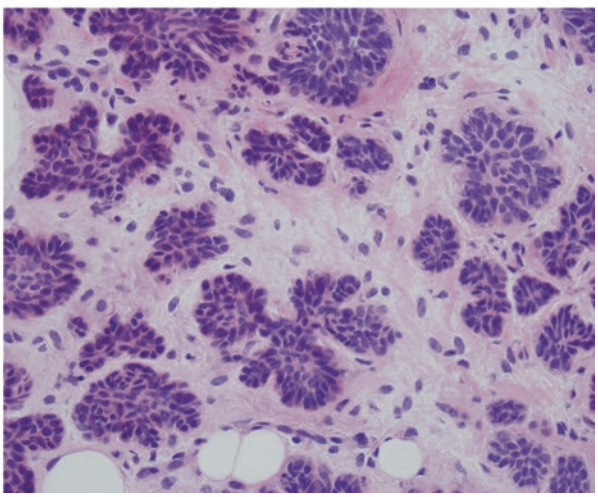
MICRONODULAR *MEDIUM* 7-64

- Rounded silhouette
- Dermis and subcutaneous fat



MYXOID *HIGH* 7-65

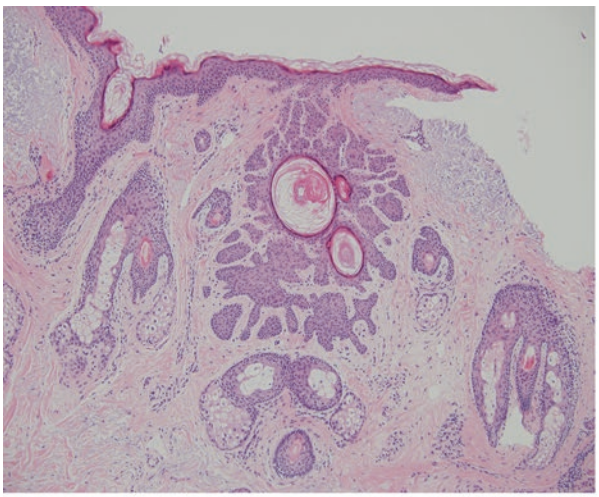
- Paucicellular mucoid stroma



MICRONODULAR *HIGH* 7-66

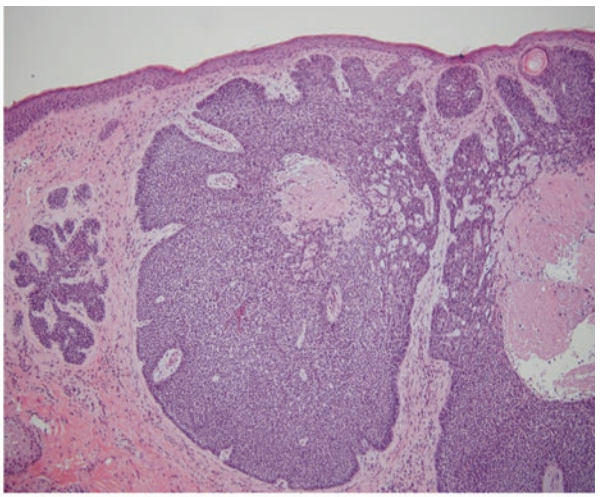
- More cellular stroma
- Floret-like and small rounded basaloid foci

Challenges
Basaloid Follicular Hamartoma (BFH) vs. Nodular



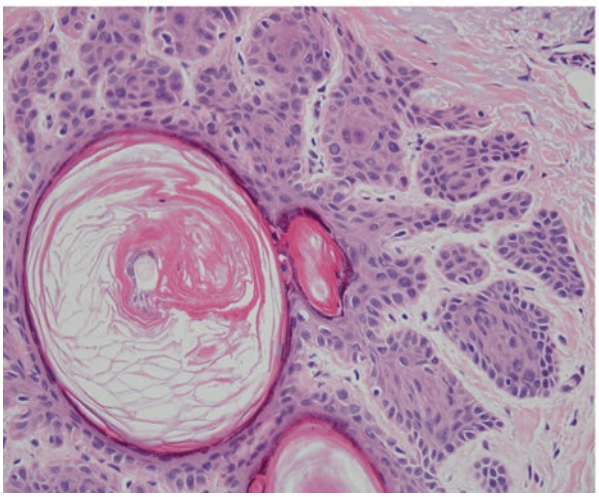
BFH *MEDIUM* 7-67

• Discrete symmetrical arrangement



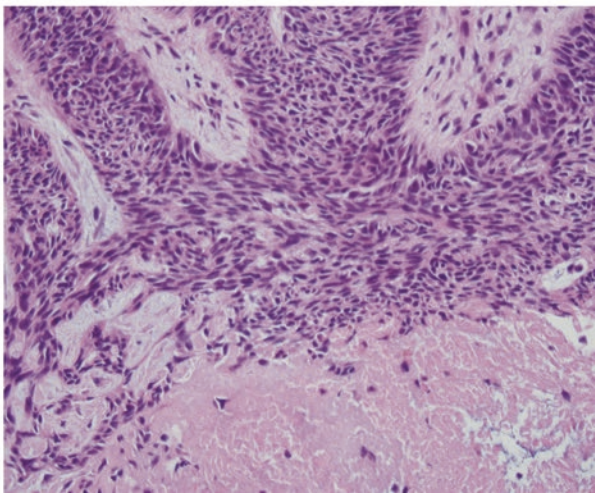
NODULAR *MEDIUM* 7-68

• Multifocal asymmetric neoplasm



BFH *HIGH* 7-69

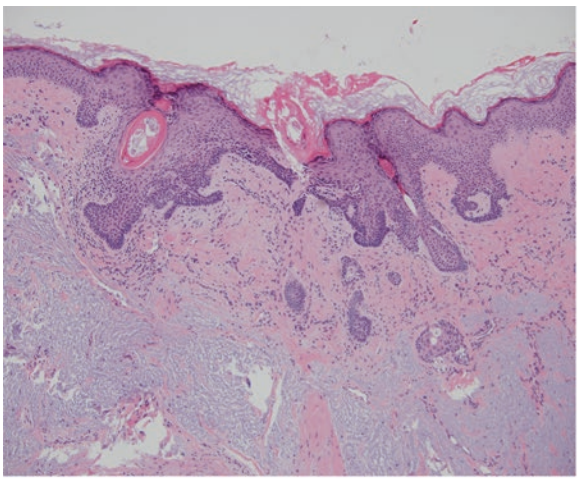
• Radial array of secondary follicles with central cystic cavity



NODULAR *HIGH* 7-70

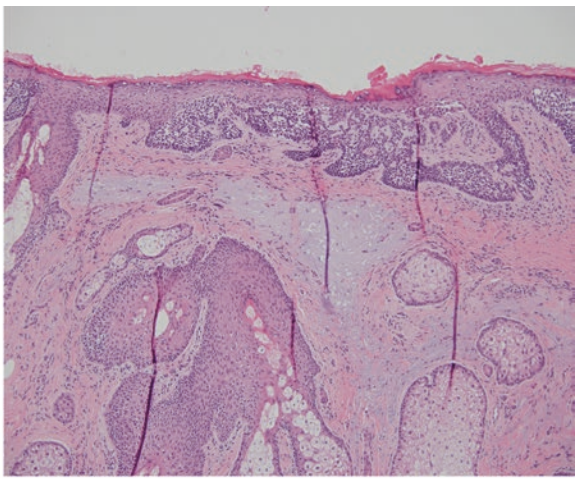
• Undifferentiated basaloid neoplasm with increase mitoses and necrosis

Challenges
BCC with Follicular Extension vs. Superficial BCC



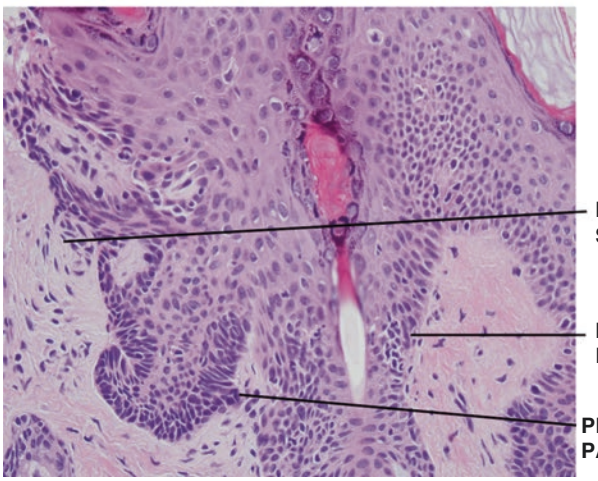
BCC WITH FOLLICULAR EXTENSION 7-71

- Focal or multifocal follicular involvement
- Involvement of the superficial dermis



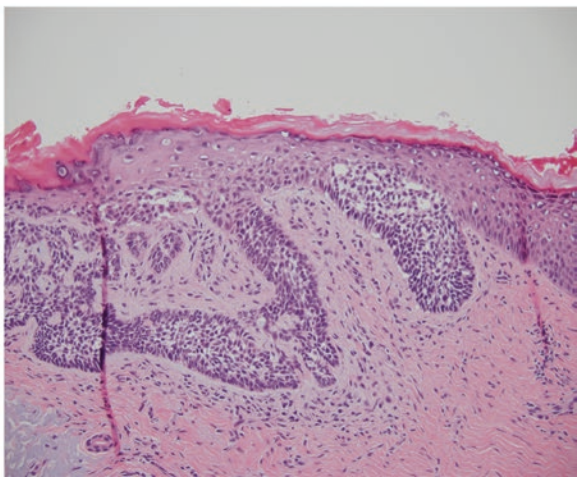
SUPERFICIAL *MEDIUM* 7-72

- Focal or multifocal follicular extension
- Involvement of the superficial dermis



BCC WITH FOLLICULAR EXTENSION 7-73

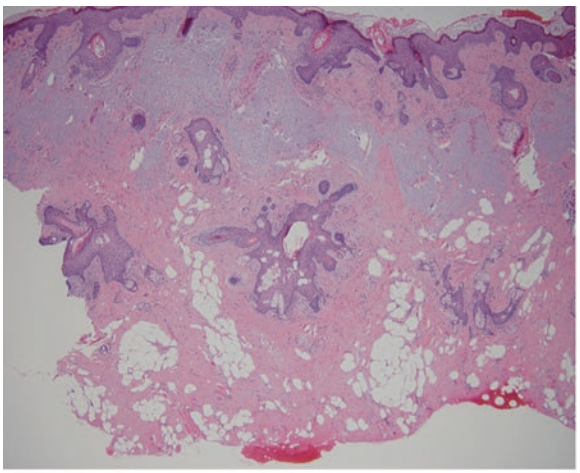
- Intimate association with native follicle
- Myxoid stroma with peripheral palisading



SUPERFICIAL *HIGH* 7-74

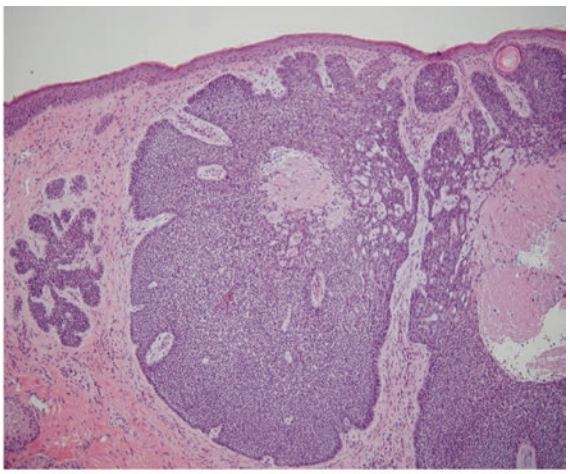
- No association with native follicles

Challenges
Funny Follicle vs. Nodular BCC



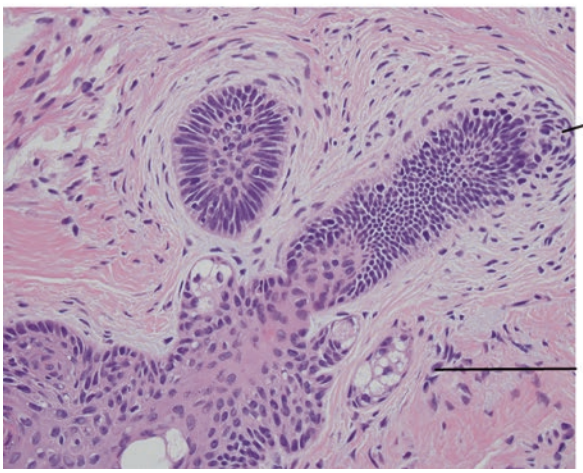
FUNNY FOLLICLE *LOW* 7-75

- Deep dermal location
- Complex branching arrangement



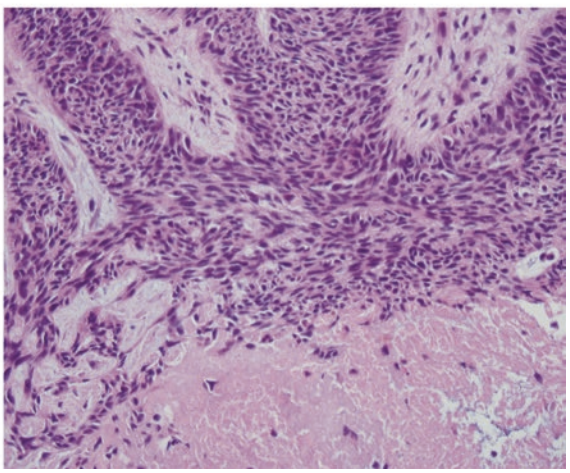
NODULAR *MEDIUM* 7-76

- Connection with epithelium
- Rudimentary irregular rounded silhouette



FUNNY FOLLICLE *HIGH* 7-77

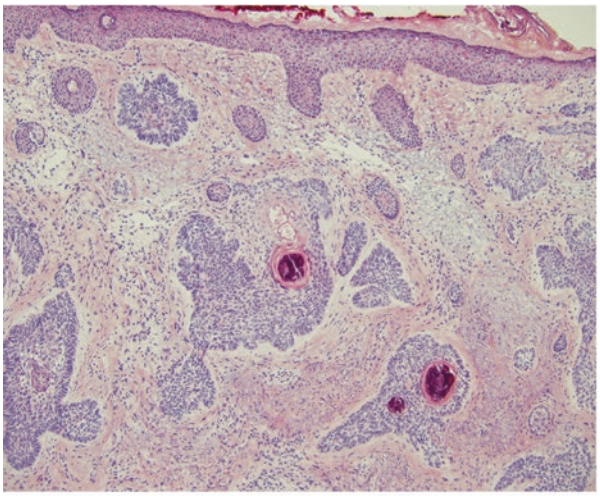
- Advanced follicular differentiation with sebaceous lobules and dermal papillae
- Deeper cuts often show clear follicular differentiation, or loss of the follicle



NODULAR *HIGH* 7-78

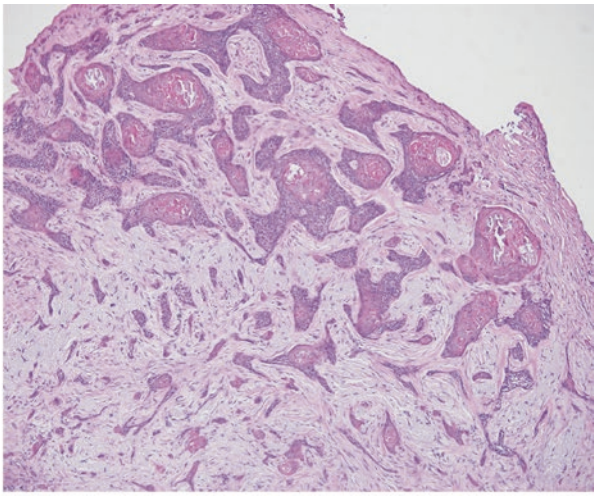
- Primordial and rudimentary basaloid foci with necrosis
- Deeper cuts will show persistence of the tumoral foci

Challenges
Keratinizing BCC vs. Basosquamous Carcinoma



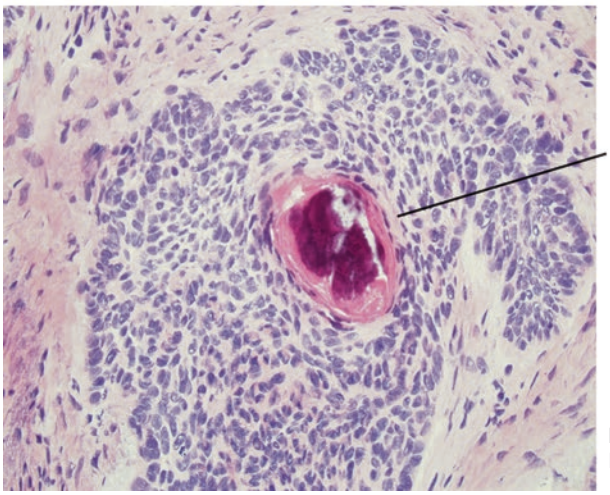
KERATINIZING BCC *MEDIUM* 7-79

• Rounded basaloid tumor foci with central keratinization



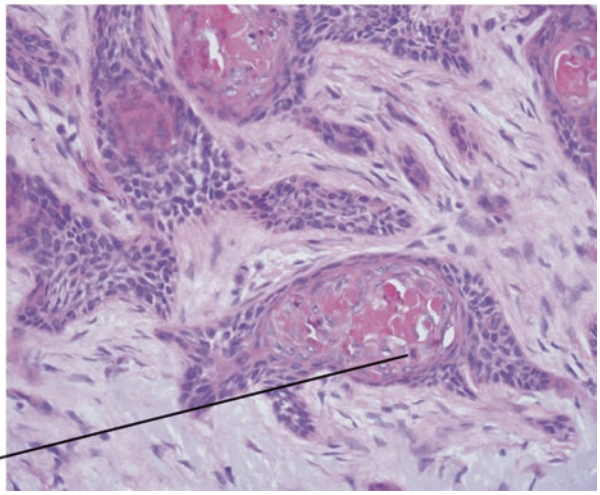
BASOSQUAMOUS CARCINOMA *MEDIUM* 7-80

• Irregular basaloid and squamous foci



KERATINIZING BCC *HIGH* 7-81

• Central keratinizing foci showing mature keratin c/o malignant squamous cells



BASOSQUAMOUS CARCINOMA *HIGH* 7-82

• Central keratinizing foci with malignant squamous cells

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2. Miller D, Weinstock M. Non-melanoma skin cancer in the United States: incidence. J Am Acad Dermatol. 1994;30:774–8.
3. Pathology of basal cell carcinoma. In: Weedon D, editor. Skin pathology, 2nd ed. London: Churchill Livingstone; 2002.

Adnexal Neoplasms

8

Michael B. Morgan

The cutaneous adnexae broadly encompass appendageal structures of the skin including the follicle and associated sebaceous and apocrine glands as well as the eccrine sweat apparatus. Each of these structures can be subdivided on the basis of anatomic location, structure and function. Moreover, each of these subdivisions may give rise to benign or malignant neoplasms. These tumors will be discussed herein.

The adnexal neoplasms may be elementally thought of as caricatures of their derived anatomic structures imbued with phenotypic and genotypic attributes similar to their corresponding mature/developed adnexal counterpart. This chapter will deal with the most important eccrine and follicular benign adnexal neoplasms. Sebaceous and apocrine lesions will be accorded special consideration in Chapter 11.

The eccrine apparatus is found throughout the integument and consists of a complex series of coiled and straight glandular elements that originate in the deep dermis and subcutaneous fat coursing through the dermis as ducts to receive the epithelium as the acrosyringia. The glandular component comprises two cell types, one dark and the other light in appearance, that serve as a useful reminder of the important tumoral constituency of the deep dermal glandular-derived eccrine spiradenoma and cylindroma. The latter tumor often shows a close tumoral approximation whose disposition is likened to the appearance of a jigsaw puzzle. Such adnexal tumors may in turn derive from the ductular portion of the eccrine apparatus, giving rise to the hidradenoma/acrospiroma or the benign mixed tumor otherwise referred to as chondroid syringoma. Similarly, derivation from the upper dermal duct is the putative source of syringoma and as such is comprised of tadpole or tear-drop shaped glands with ducts. Finally, derivation from the acrosyringial duct is thought to be the source of poroma, producing a horizontally disposed neoplasm with uniform basaloid cells punctuated by eccrine ducts or pores. While each of these benign neoplasms may give rise to or be represented by their respective malignant counterparts, discussion of this topic will be forthcoming.

Likewise, the follicle is a complex multifunctional apparatus comprising the basilar germinative portion of the hair shaft that gives rise to the pilomatricoma, the middle isthmic portion bounded by the erector pilae muscle inferiorly and sebaceous duct superiorly, the source of tricholemmoma, and, finally, the normal keratinized upper portion termed the infundibulum. Pilomatricoma, faithful to its germinative origins, shows a basaloid highly proliferative component with hair-like abrupt keratinization and ghost cells. The most important benign simulants of basal cell carcinoma, known collectively as trichoblastoma or trichoepithelioma, principally derive from the isthmus and basilar portions of the follicle. As such, variable differentiation towards the lumen (ductular), outer root sheath, inner root sheath and the base (follicular germs) may be seen.

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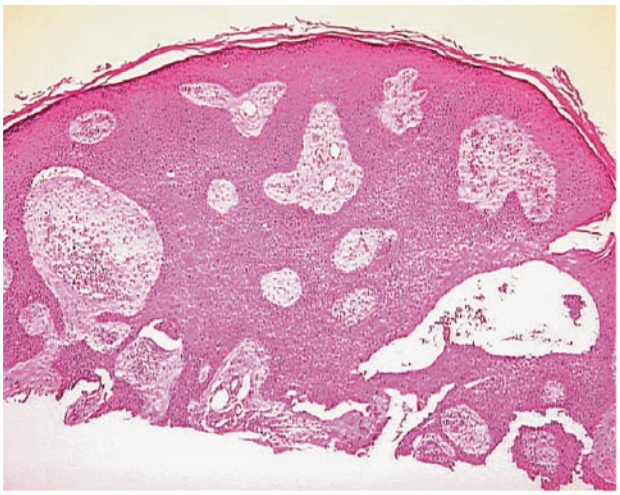
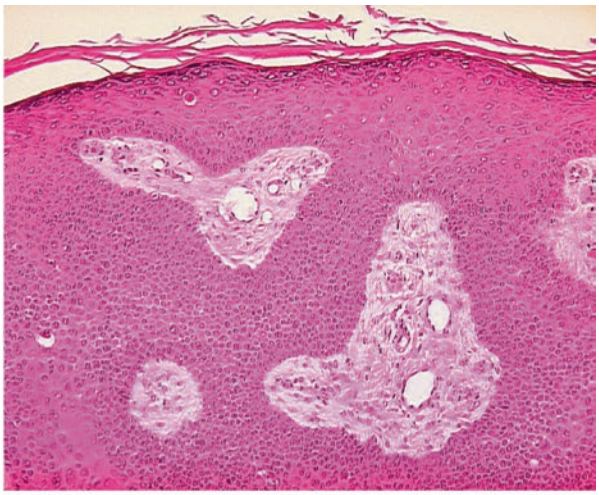
M. B. Morgan et al. (eds.), *Atlas of Mohs and Frozen Section Cutaneous Pathology*,
https://doi.org/10.1007/978-3-319-74847-4_8

Poroma



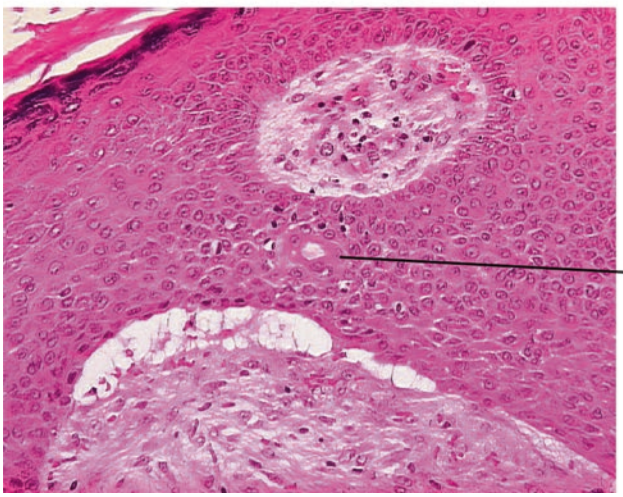
LOW 8-1

- Plate like horizontal arrangement of epithelial cells



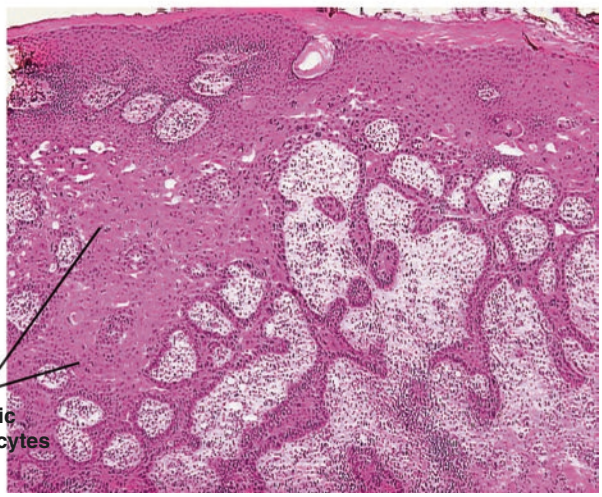
MEDIUM 8-2

- Sheets of uniform epithelial cells with prominent fibrovascular cores



HIGH 8-3

- Intraepithelial pores or ducts



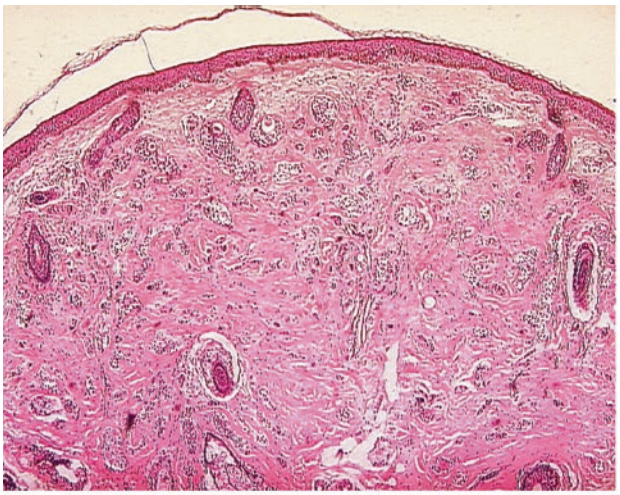
ACRAL SQUAMOUS CELL CARCINOMA 8-4

- Acral SIS often confused with poroma

Note: Keratinocyte dysplasia and lack of pores

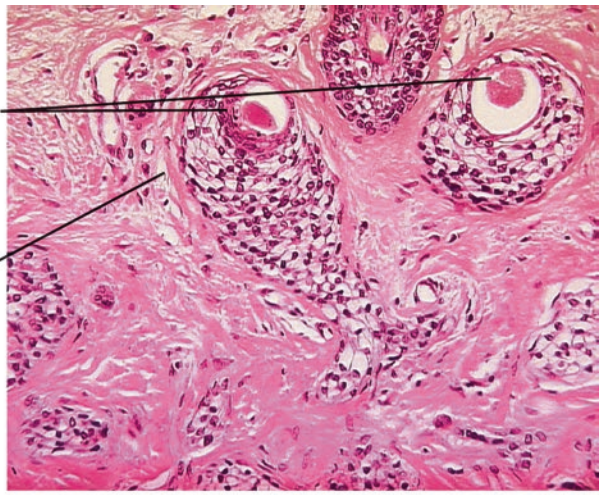
Syringoma/Microcystic Adnexal Carcinoma

SYRINGOMA



LOW 8-5

- Superficial delimited neoplasm

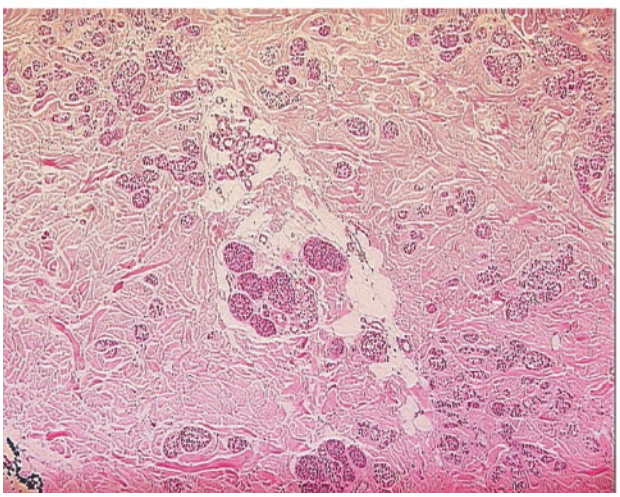


HIGH 8-6

- Detail of tear-drop and comma shaped ducts

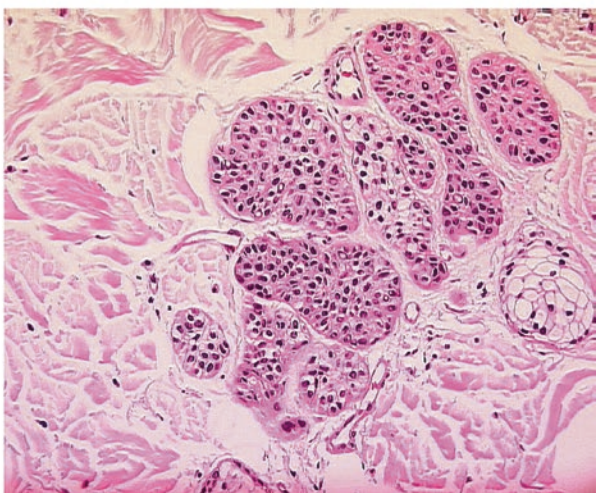
Note: Inspissated contents

MICROCYSTIC ADNEXAL CARCINOMA



LOW 8-7

- Deep extension of tumor throughout dermis

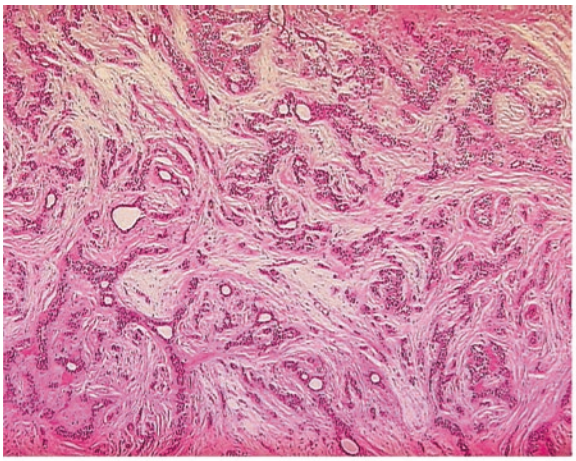


HIGH 8-8

- Solid nodules of keratinocytes with dysplastic cells
- Limited glandular differentiation

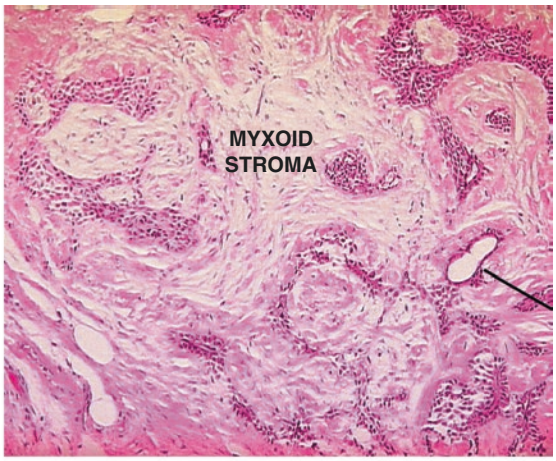
Note: Absence of ducts/glands

Benign Mixed Tumor



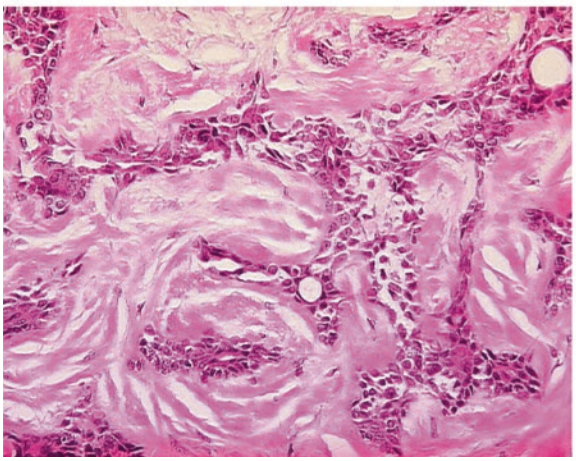
LOW 8-9

- Biphasic proliferation of glands and stroma



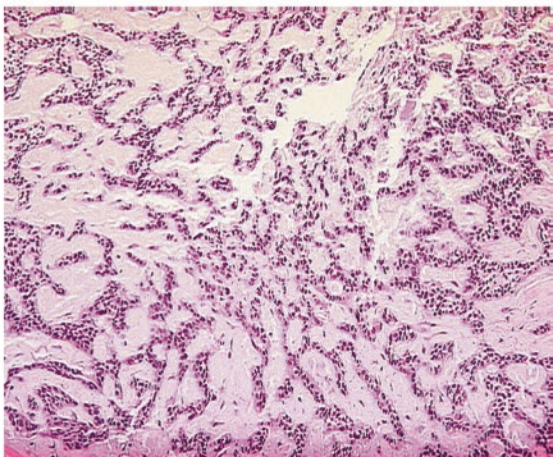
MEDIUM 8-10

Note: Glandular lumina and myxoid stroma



HIGH 8-11

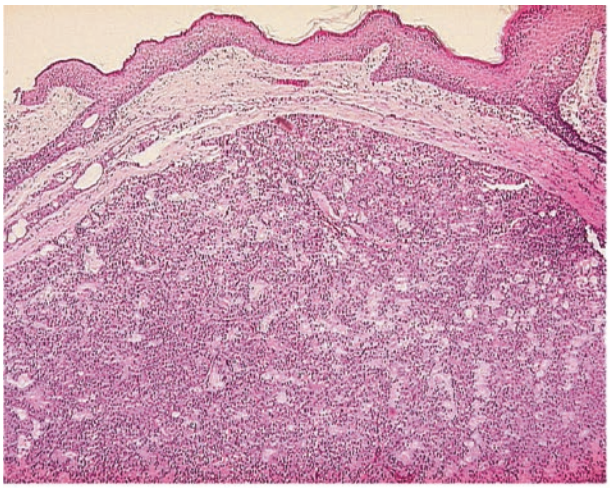
- Detail of glandular arrangement



MYXOID BCC 8-12

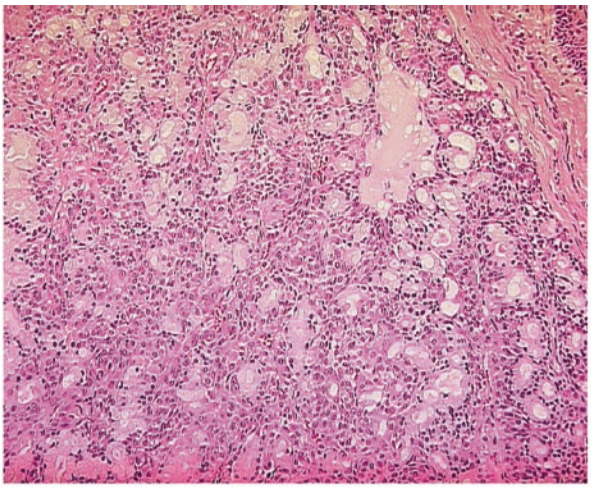
- More dispersed basaloid epithelial cells with diffuse myxoid background

Hidrandenoma



LOW 8-13

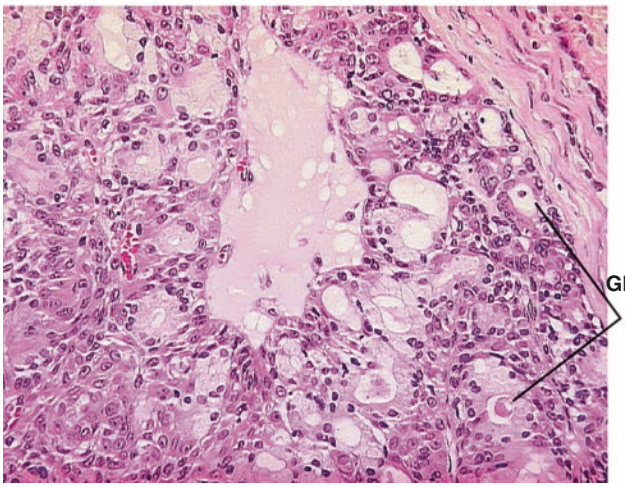
- Well circumscribed collection of dermal glands



MEDIUM 8-14

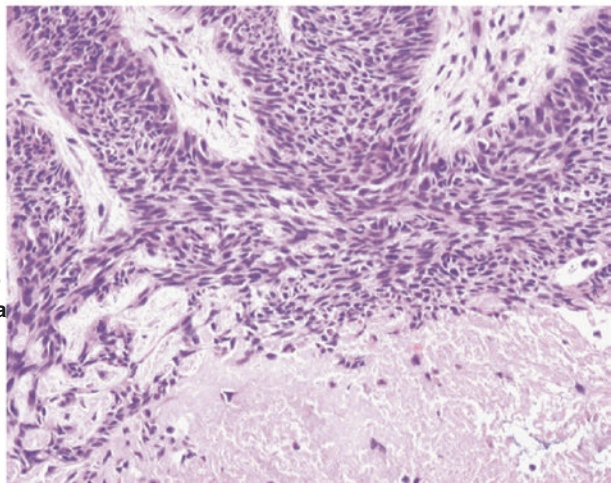
- Glandular and solid cellular foci

Note: Lack of peripheral palisading



HIGH 8-15

- Detail of glandular foci

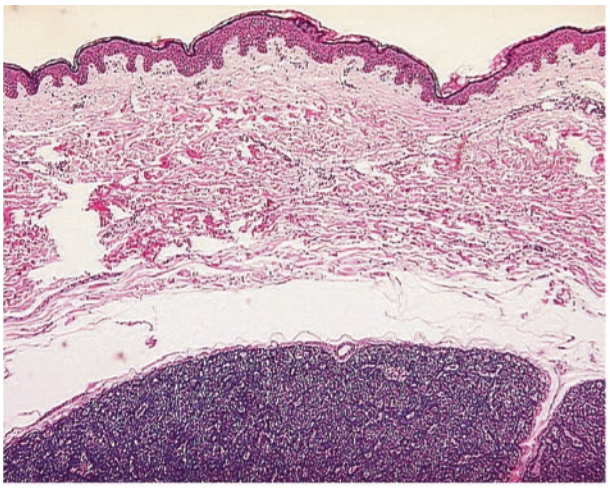


NODULAR BCC *HIGH* 8-16

- Basaloid neoplasm

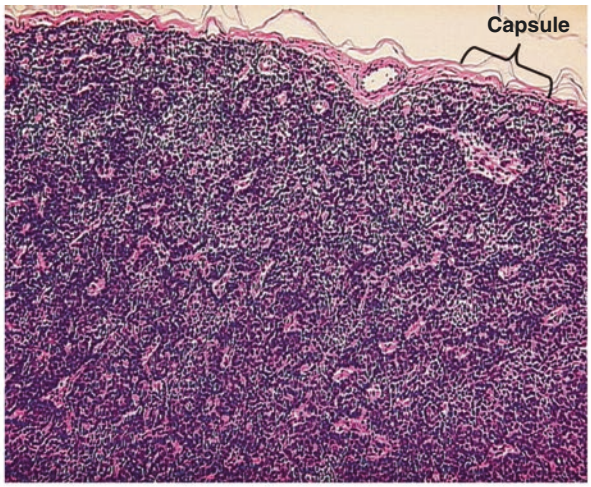
Note: Peripheral palisading

Spiradenoma



LOW 8-17

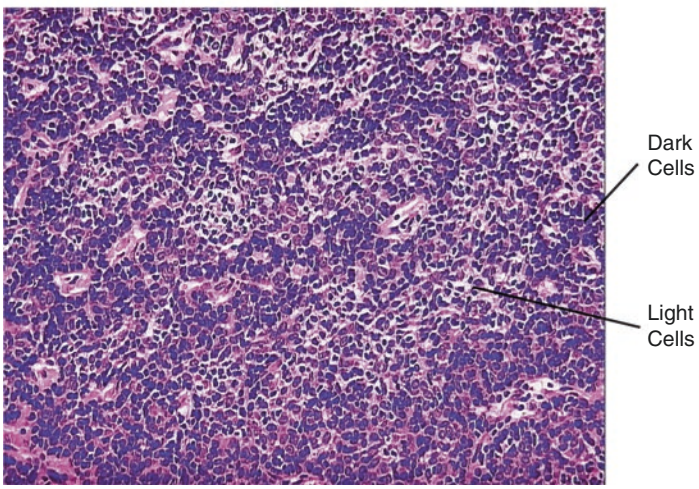
- Deep dermal unifocal well-circumscribed tumor



MEDIUM 8-18

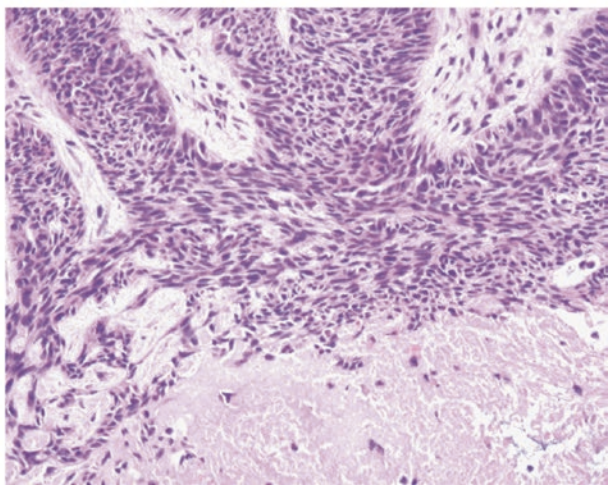
- Heterogeneous basaloid cells

Note: Absence of palisading and thin capsule



HIGH 8-19

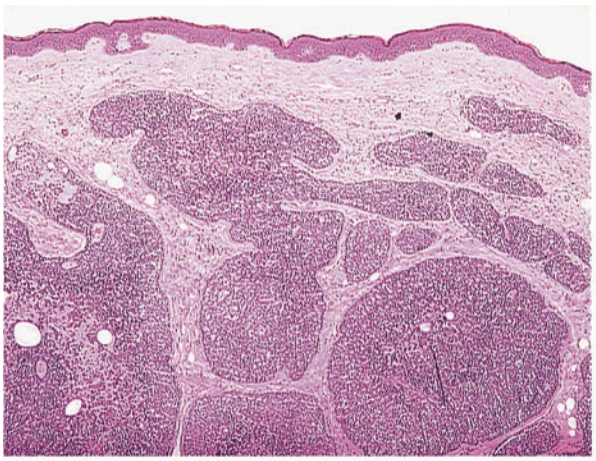
- Detail of biphasic (light and dark) cellular composition



NODULAR BCC *HIGH* 8-20

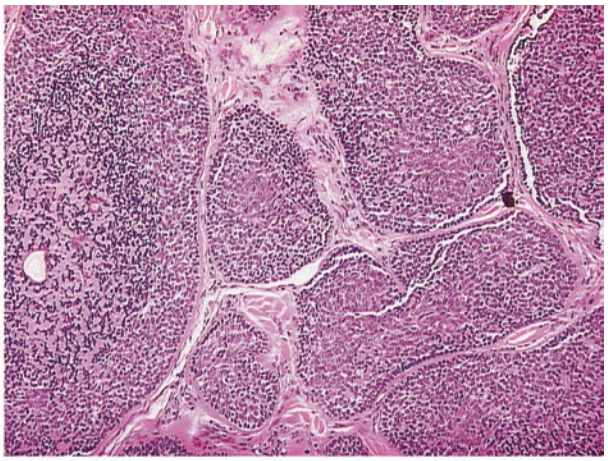
- Basaloid tumor with peripheral palisading

Cylindroma



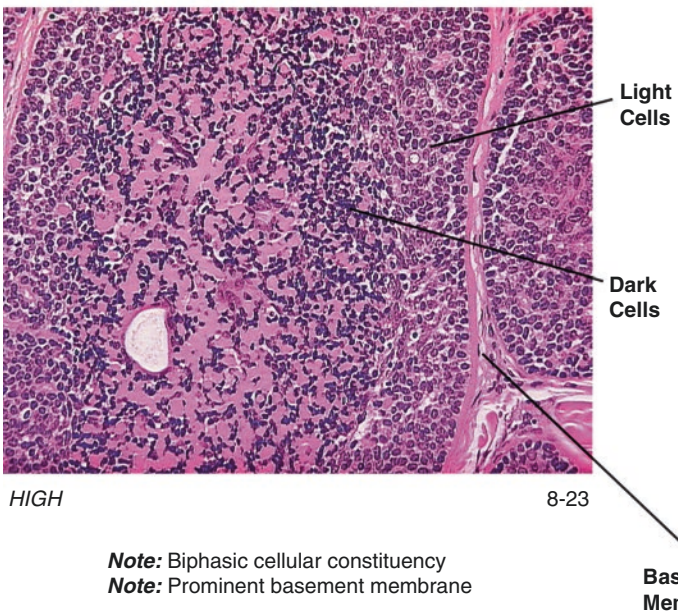
LOW 8-21

- Multifocal deep dermal basaloid neoplasm



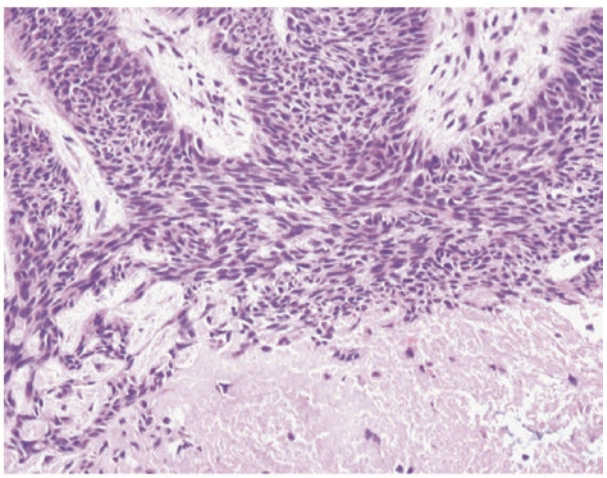
MEDIUM 8-22

- Close apposition of tumoral foci likened to jigsaw puzzle



HIGH 8-23

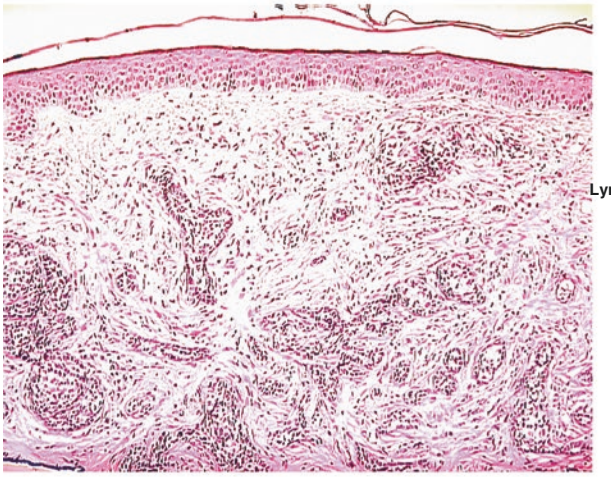
Note: Biphasic cellular constituency
Note: Prominent basement membrane



NOUDULAR BCC *HIGH* 8-24

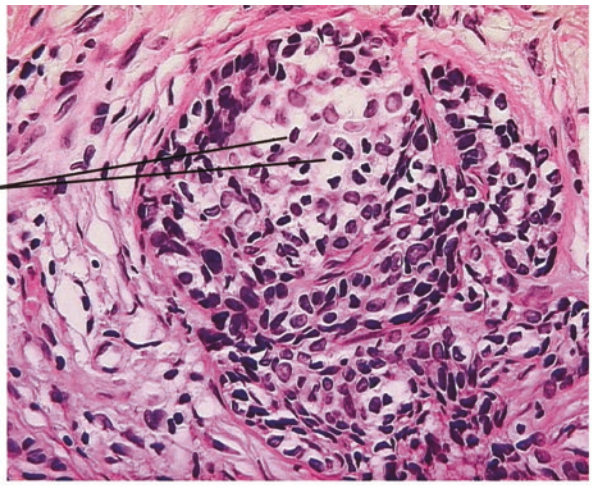
- Unifrom basaloid tumor with peripheral palisading, no basement membrane

Benign Cutaneous Lymphadenoma



LOW 8-25

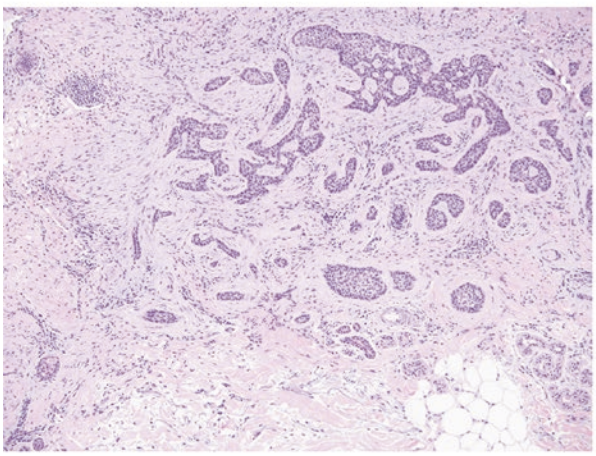
- Irregular basaloid tumoral islands containing lymphocytes



MEDIUM 8-26

- Detail of neoplasm

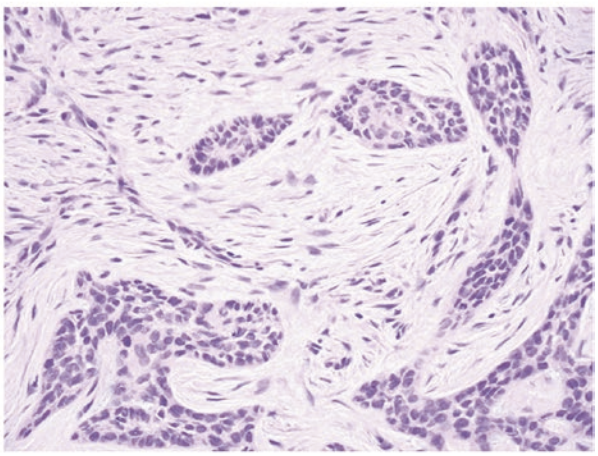
Note: Characteristic infiltration of lymphocytes and absence of clefting and palisading



INFILTRATING BCC *MEDIUM* 8-27

- Irregular infiltrative basaloid tumor

Note: Desmoplastic stroma

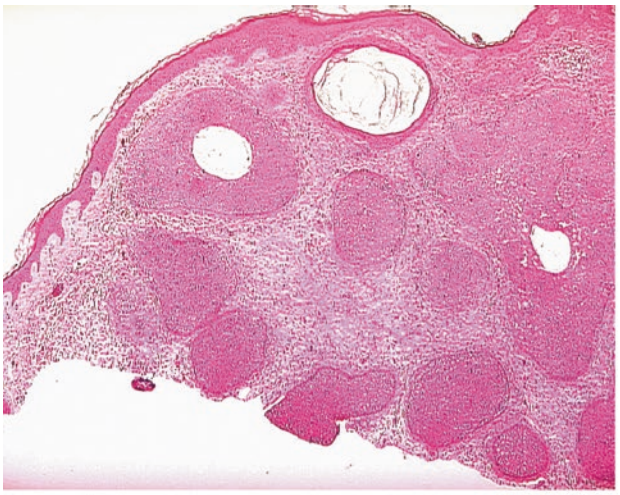


INFILTRATING BCC *HIGH* 8-28

- Detail of basaloid foci

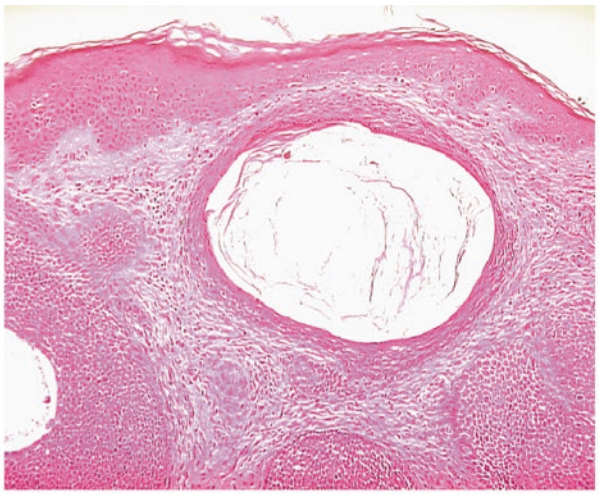
Note: Absence of lymphocytes

Large Nodular Trichoblastoma



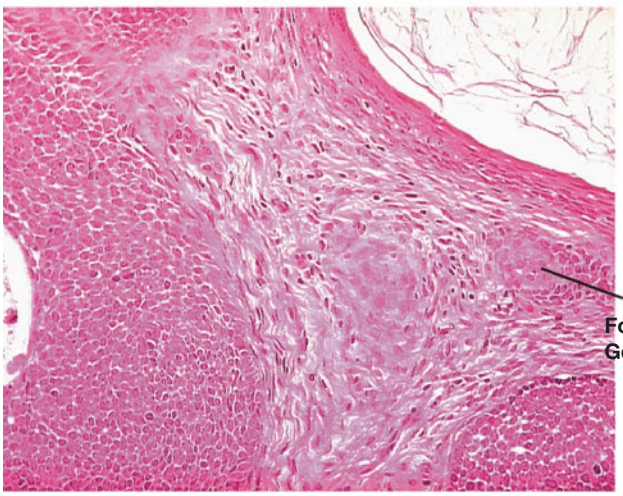
LOW 8-29

- Infiltrating large nodular basaloid foci



MEDIUM 8-30

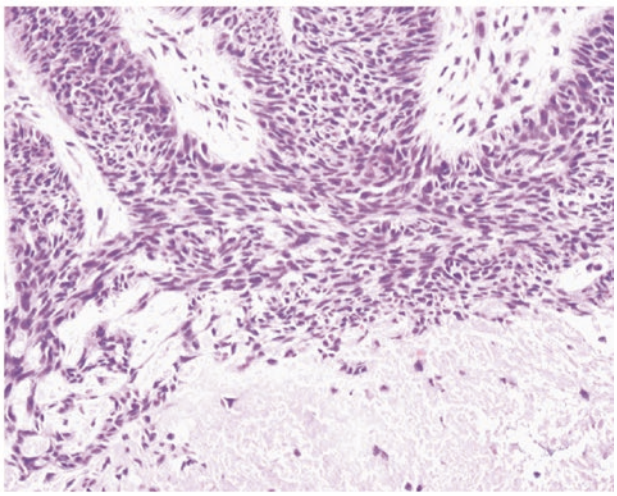
Note: The presence of cysts and cellular stroma



HIGH 8-31

- Detail of basaloid foci

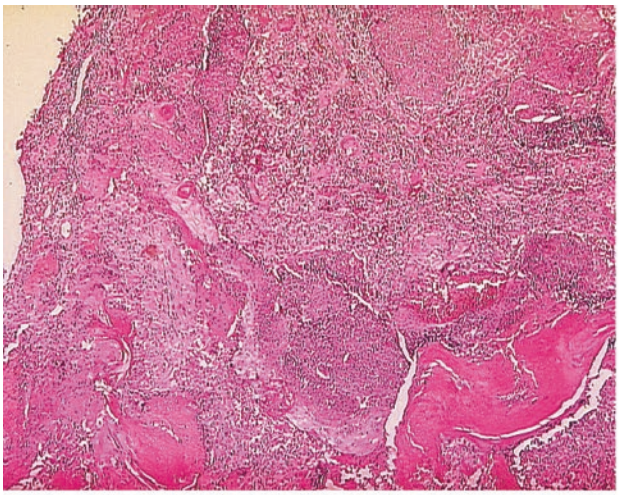
Note: Absence of palisading/clefting and the presence of follicular germs



NODULAR BCC *HIGH* 8-32

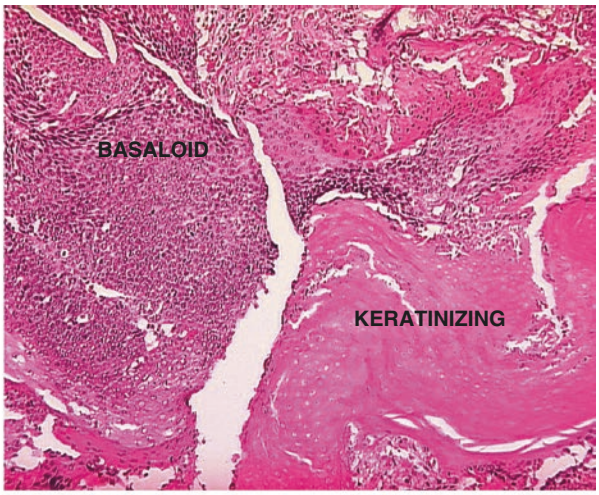
- Basaloid neoplasm without follicular differentiation

Pilomatricoma



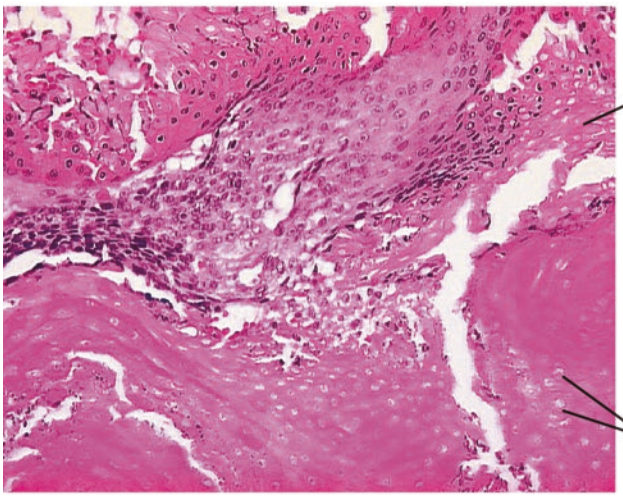
LOW 8-33

- Biphasic neoplasm



MEDIUM 8-34

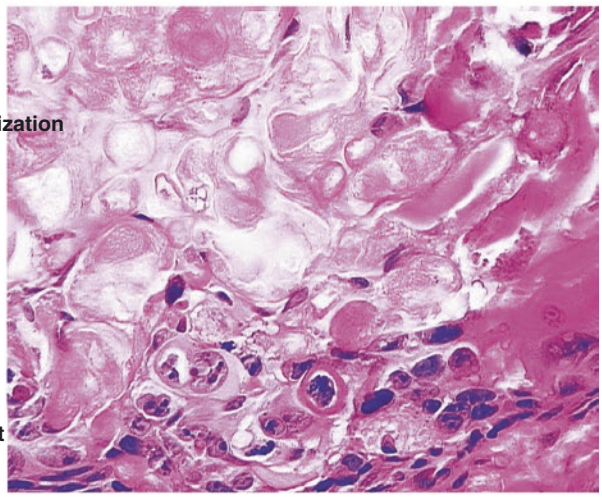
- Detail of basaloid and keratinized foci



HIGH 8-35

- Detail of matricial differentiation

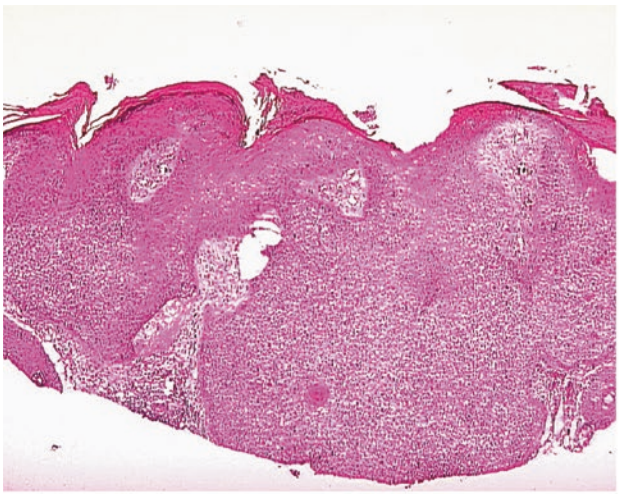
Note: Ghost cells and abrupt keratinization



MATRICIAL CARCINOMA 8-36

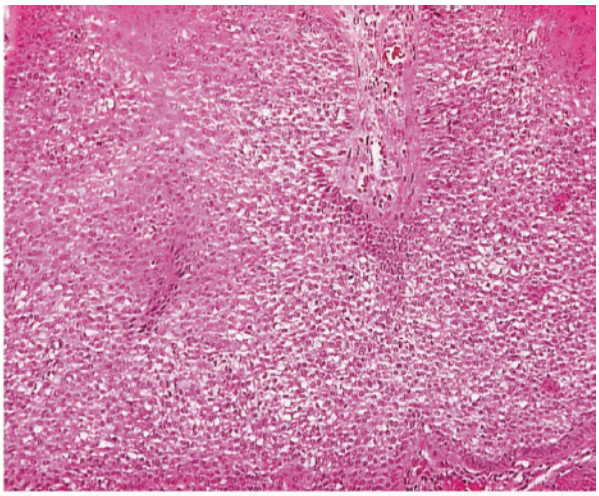
- Detail of matricial differentiation with malignant keratinizing cells

Tricholemmoma



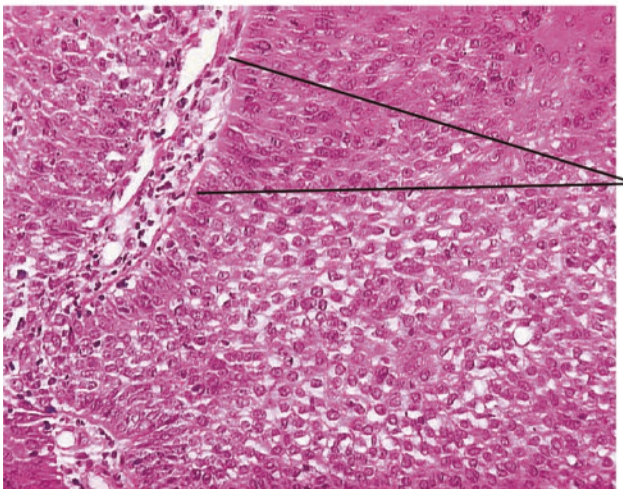
LOW 8-37

- Vertically oriented clear cell neoplasm with epidermal connection



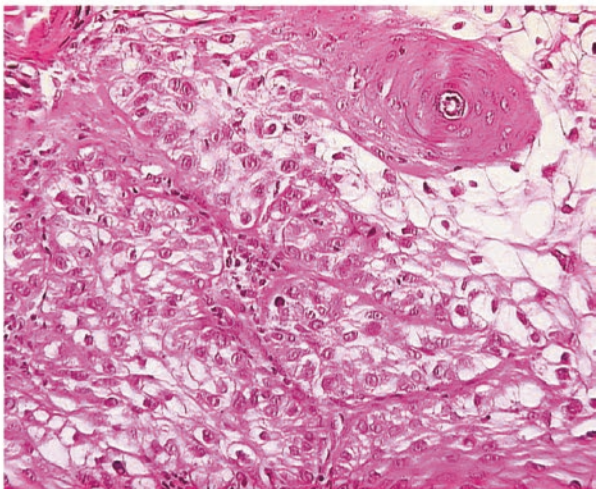
MEDIUM 8-38

- Uniform population of clear (glycogenated) cells



HIGH 8-39

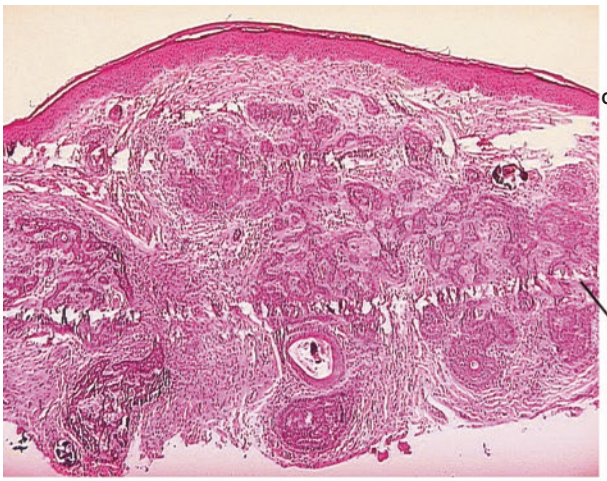
Note: Tendency to peripherally palisade



TRICHILEMMAL CARCINOMA 8-40

- Clear cell squamous carcinoma with trichilemmal differentiation

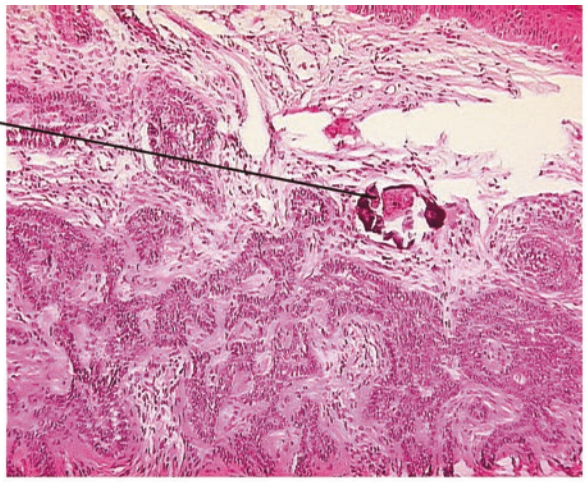
Trichoepithelioma



LOW 8-41

- Complex basaloid tumor with abundant stroma

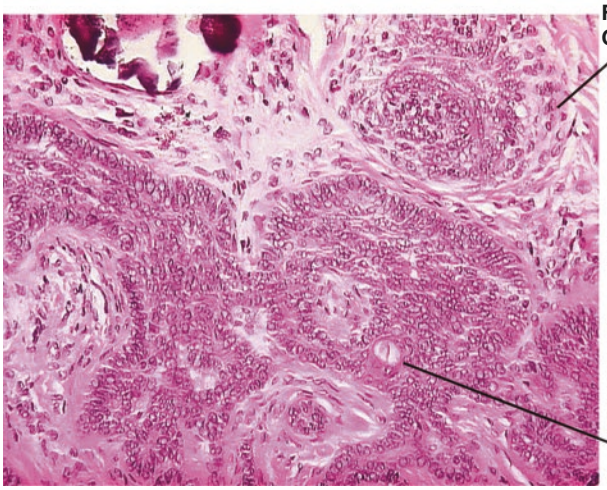
Note: Horizontal streak artifact produced by retained calcification



MEDIUM 8-42

- Complex fenestrated array of basaloid foci

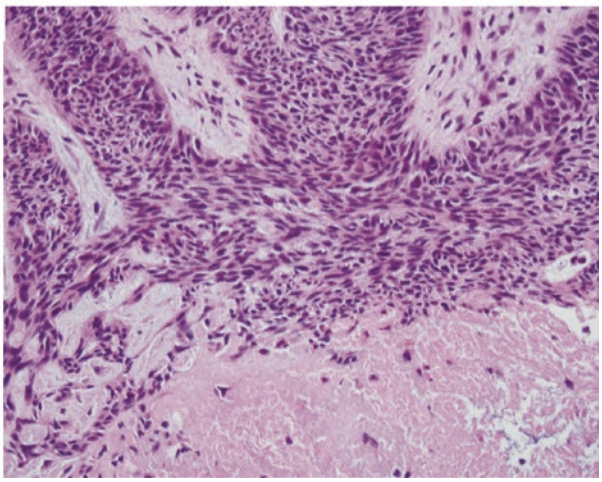
Note: Calcification (uncommon in BCC)



HIGH 8-43

- Detail of basaloid foci

Note: Ductules and follicular germs



NODULAR BCC *HIGH* 8-44

- Uniform population of basaloid cells without ductules or follicular germs

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Malignant Adnexal Neoplasms

9

Ryan S. Jawitz and Jack C. Jawitz

Malignant adnexal neoplasms are rare tumors derived from apocrine, eccrine, sebaceous and follicular adnexal structures. Herein, the malignant tumors of eccrine differentiation will be reviewed. The histological features that distinguish these neoplasms from each other and from benign tumors, as well as the features that are found when these tumors locally invade neighboring tissue and/or metastasize, are discussed.

Despite several attempts to organize the nuances and subtleties of malignant adnexal carcinomas, no universal agreement as to classification exists. Furthermore, little rationale exists to separate among them as treatment protocol and/or prognosis does not vary among them. Herein, we will only discuss the most well-recognized eccrine adnexal carcinomas and how they are distinguished from their benign counterparts. Common synonyms or generally accepted alternative names are provided.

Malignant Eccrine Poroma (Porocarcinoma, Malignant Acrospiroma) is rare, but it is the most common sweat duct carcinoma. It arises from the acrosyringa, and clinically presents on the extremities as a blue/black nodule, or plaque, which may be ulcerated. The malignant form is only rarely found in association with its benign form, the eccrine poroma. In distiguishing among them, the malignant eccrine poroma exhibits pronounced cytologic atypia, smaller, more basophilic staining cells, an increased mitotic rate and a deeply infiltrative silhouette.

Microcystic Adnexal Carcinoma (MAC, Sclerosing Sweat Duct Carcinoma) is most commonly found on the upper lip or nose. Clinically, MAC presents as a deeply indurated and slow growing plaque. Histologically, its superficial portion often resembles a benign syringoma with ducts, keratinous cysts and small cords of cells. The deeper component exhibits nests and basaloid strands of duct like cells with or without lumina embedded in a dense stroma. MAC is most easily distinguished from a benign syringoma and the benign plaque syringoma by its deep dermal infiltration.

Syringoid Carcinoma (Syringoid Eccrine Carcinoma) is usually found on the scalp, trunk or extremities, presenting as a plaque or nodule. Histologically, syringoid carcinoma resembles the benign syringoma possessing tear-drop and comma shaped ducts surrounded by dermal stroma. The syringoid carcinoma additionally shows increased anaplasia, cellularity and deep invasiveness. Differentiation can be made from: basal cell carcinoma, by the presence of true ductal differentiation and lack of palisading tumor cells; from microcystic adnexal carcinoma, by its lack of tumor stranding and solid tumoral foci and keratin-filled cysts.

Hidradenocarcinoma (Malignant Hidradenoma, Malignant Acrospiroma) is a rare malignant tumor thought to be eccrine, but many have apocrine gland features (apoeccrine differentiation). These are found most commonly on the face and extremities, but can present anywhere on the skin, clinically as a dermal nodule. Eccrine differentiation features small basophilic poroid cells with interspersed luminal ducts. Apocrine features include glandular columnar cells with decapitation secretion as well as ducts lined with eosinophilic cuticles. Malignancy is histologically defined by deep dermal extension with infiltrative borders and lack of circumscription, and tumor composed of scattered atypical

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M. B. Morgan et al. (eds.), *Atlas of Mohs and Frozen Section Cutaneous Pathology*,
https://doi.org/10.1007/978-3-319-74847-4_9

cells, increased mitosis, perineural invasion, vascular invasion and tumor necrosis.

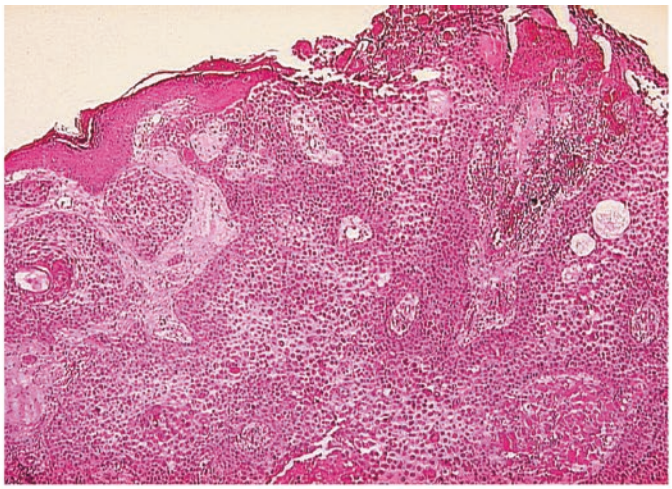
Poorly differentiated tumors with ductal differentiation are classified as not otherwise specified (NOS). In one study these tumors represented 12–16% of the ductal tumors.

Adenoid cystic carcinoma is found on the scalp, chest or vulva, usually presenting as a dermal nodule or plaque. Histologically, it resembles an adenoid cystic carcinoma of the salivary gland containing mucinous glandular proliferations with basophilic cells, arranged in cribiform ("swiss cheese") or adenoid patterns. This tumor has a propensity to extend perineurally. It may locally recur, but it rarely metastasizes.

Primary Mucinous Carcinoma (Adenocystic Carcinoma, Colloid Carcinoma) is usually found on the head and neck with 40% occurring on the eyelid. Clinically appearing as a round nodule, they may poorly present as ulcerated nodules. It must be differentiated from a cutaneous metastasis, especially mucinous carcinoma derived from the stomach appendix, breast, lung or prostate. Histological criteria for diagnosis include small islands of basophilic ductal structures with large areas of mucin (blue-tinged extracellular matrix) separated by fibrous septae. While not always present, myoepithelial cells as confirmed by immunohistochemistry within the tumor is a helpful diagnostic clue in separating the primary tumors from metastases that typically lack such cells.

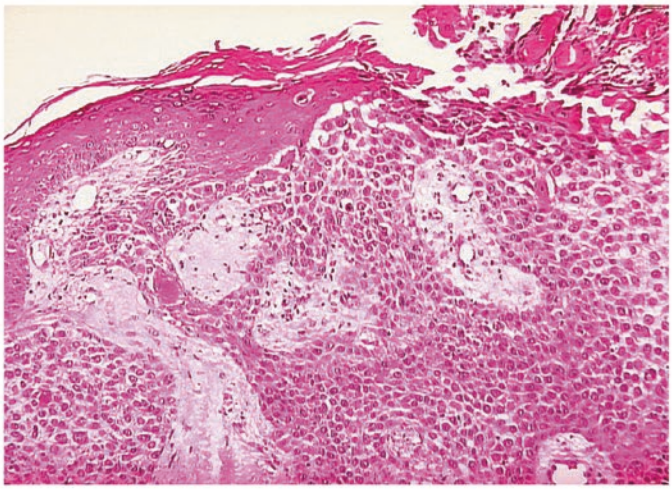
Immunohistochemistry may be resorted to differentiate these neoplasms from their visceral mimics. As most of these adnexal neoplasms show differentiation either toward adnexal lining glandular epithelium or the outer myoepithelial layer, antibodies derived to their respective components may be diagnostically exploited. Cytokeratin-7 is a useful antibody found within the normal glandular epithelium of the eccrine apparatus and malignant tumors so derived. Similarly, p63 (an analogue of p53), smooth muscle actin and S-100 may be used to demonstrate myoepithelial differentation.

Porocarcinoma



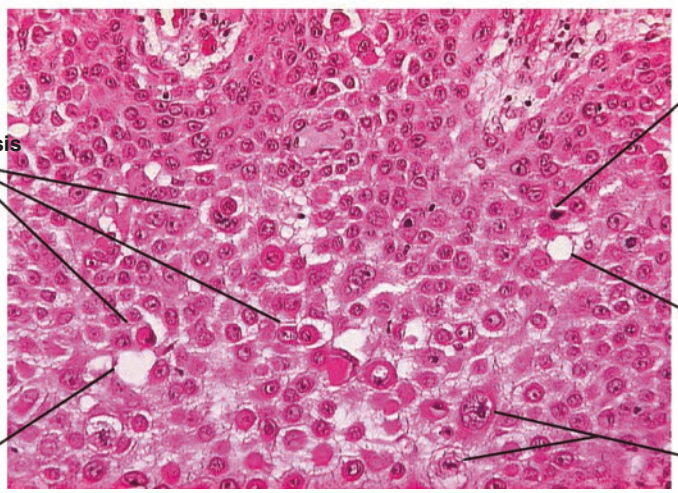
LOW 9-1

- Plate like growth pattern with superficial scale crust



MEDIUM 9-2

- Multifocal connection with the epithelium



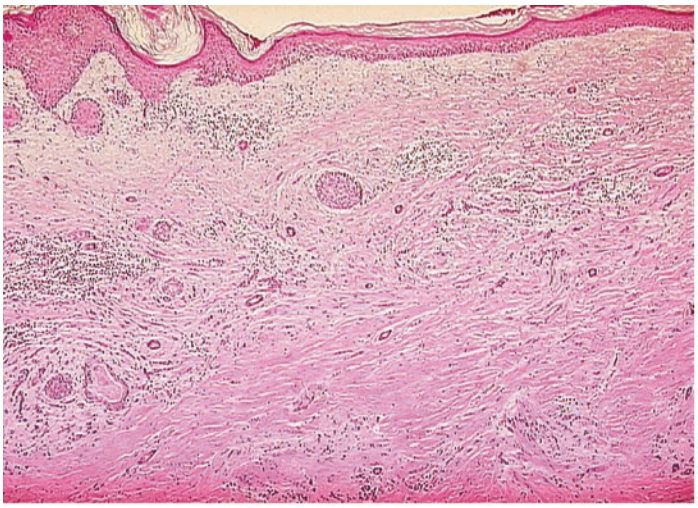
HIGH 9-3

- Sheet-like pattern comprised of dyskeratotic keratinocytes

Note: Increased mitosis and nuclear anaplasia

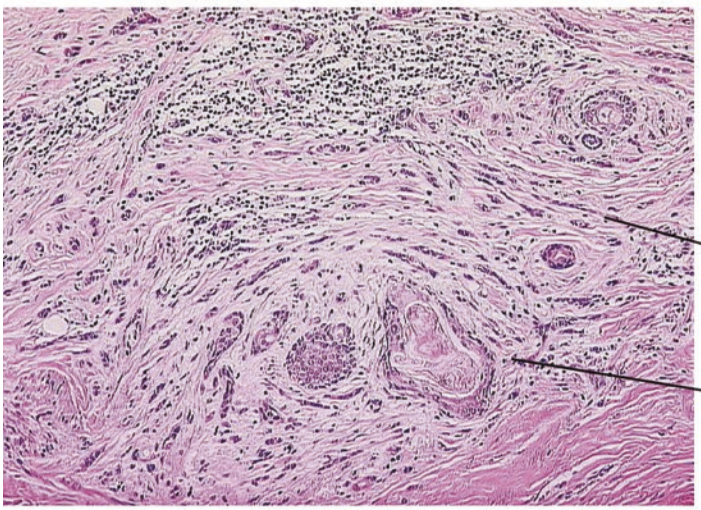
Note: Acrosyringeal ducts

Microcystic Adnexal Carcinoma (MAC)



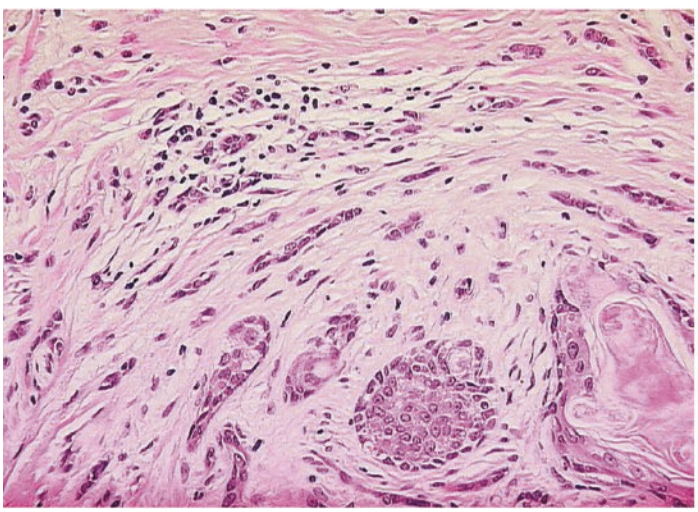
- Deeply invasive complex tumor comprised of solid cystic and stranded foci

LOW 9-4



- Detail of tumor with investing desmoplastic stroma

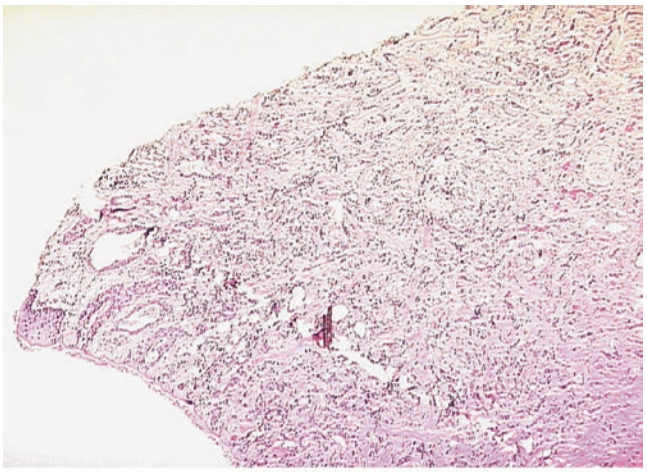
MEDIUM 9-5



- Rare tear drop shaped foci
- Most tumoral foci consist of strands and cystic foci

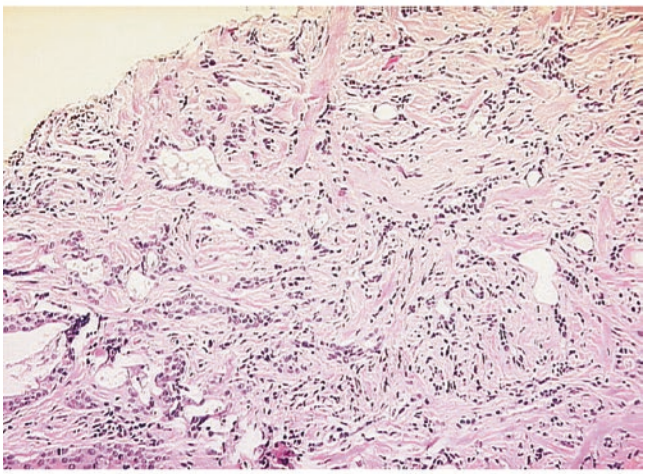
HIGH 9-6

Syringoid Eccrine Carcinoma



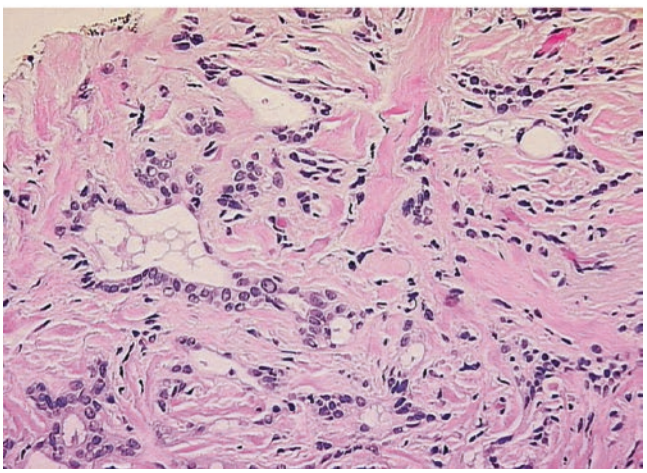
LOW 9-7

- Densely cellular deeply extending neoplasm



MEDIUM 9-8

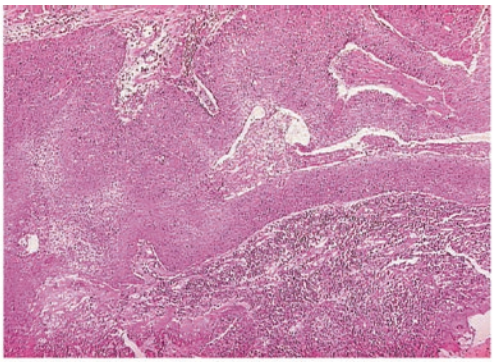
- Detail of neoplasm showing luminal differentiation



HIGH 9-9

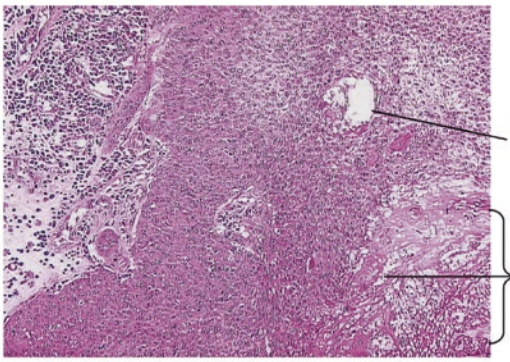
- Luminal detail with jaggedly outlined glands containing inspissated secretions

Hidradenocarcinoma



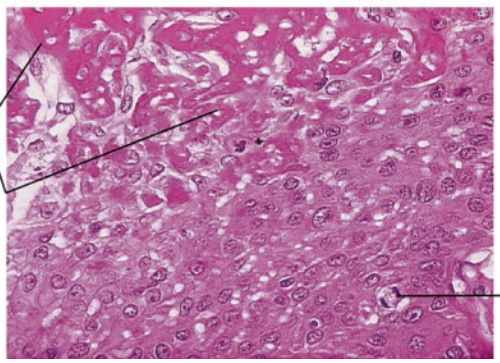
LOW 9-10

- Irregular solid and cystic neoplasm



MEDIUM 9-11

- Detail of neoplasm with geographic zone of tumor necrosis and interspersed glandular lumina

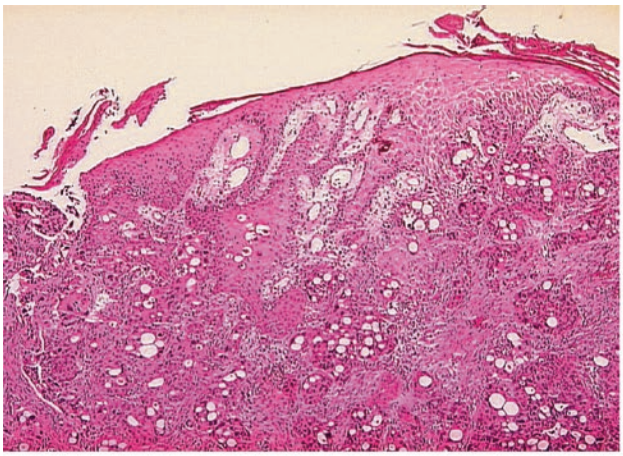


HIGH 9-12

- Detail of neoplasm comprised of hyperchromatic nuclei

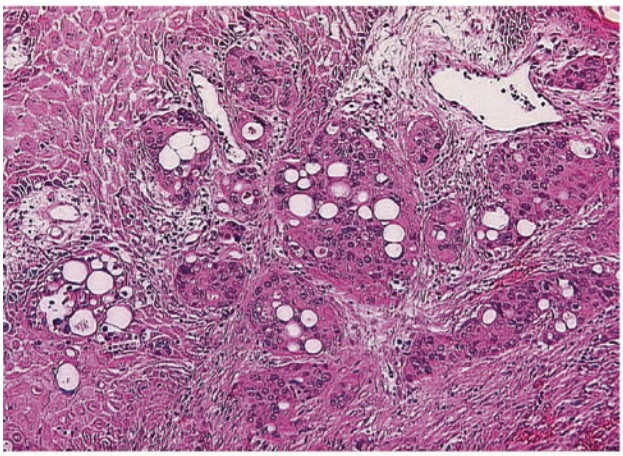
Note: Tumor necrosis
Note: Mitotic figure

Adenoid Cystic Carcinoma



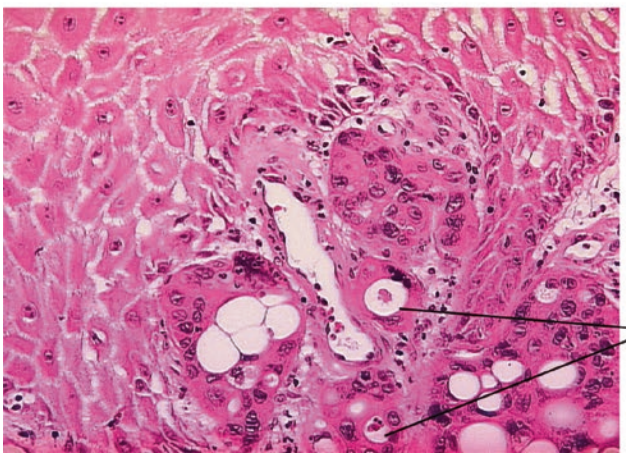
LOW 9-13

- Invasive poorly differentiated neoplasm showing intimate connection with the epithelium



MEDIUM 9-14

- Detail of neoplasm showing multicystic configuration

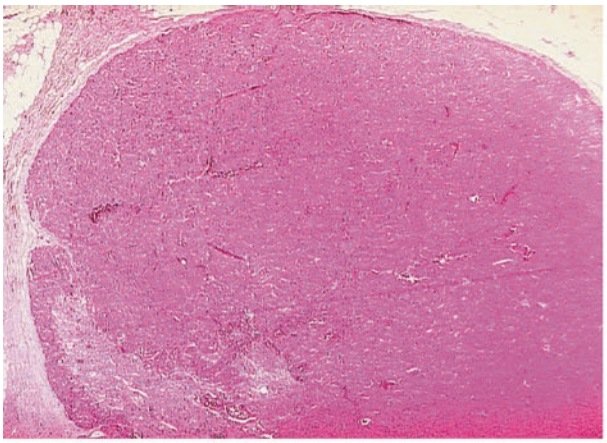


HIGH 9-15

- Detail of cystic change

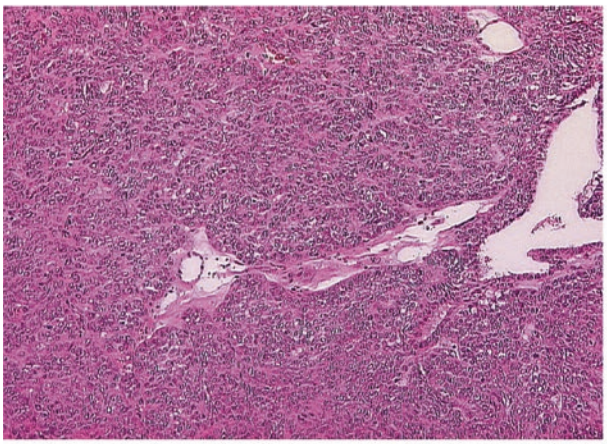
Note: Intraluminal secretions

Eccrine Carcinoma (not otherwise specified)



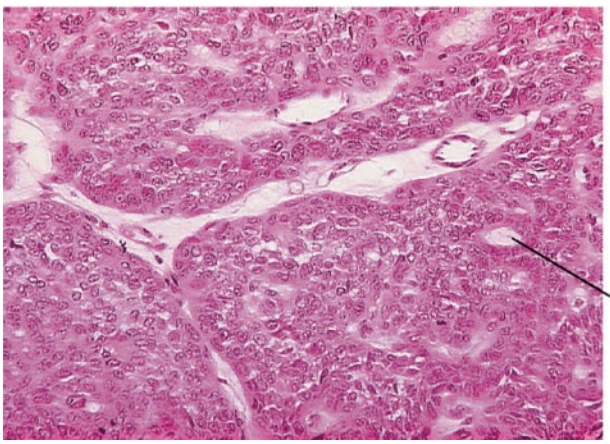
LOW 9-16

- Rounded cellular neoplasm



MEDIUM 9-17

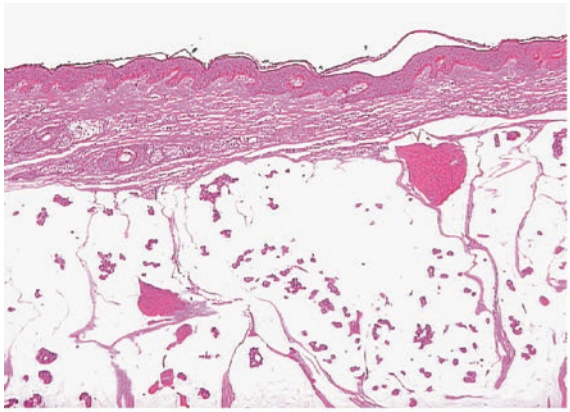
- Detail of neoplasm with solid and cystic foci



HIGH 9-18

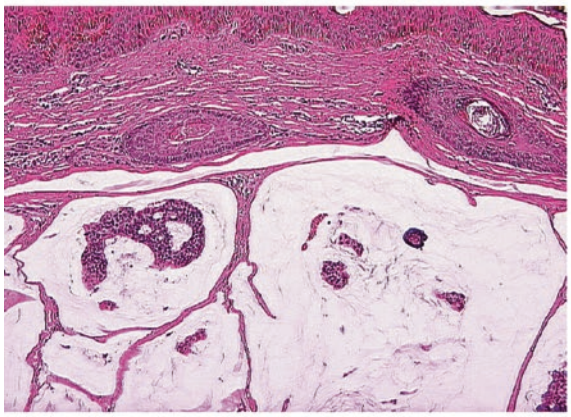
- Non-palisading tumor with intratumoral glandular foci

Mucinous Carcinoma



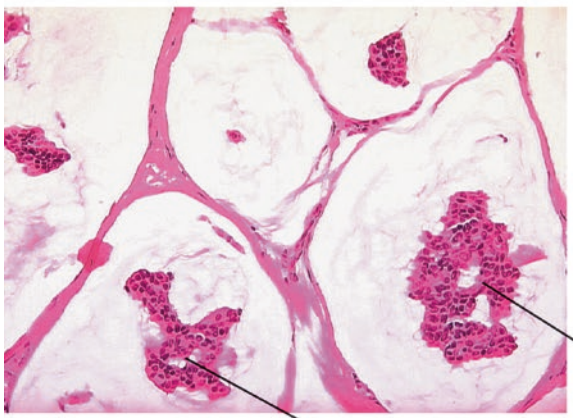
LOW 9-19

- Circumscribed dermal mass consisting of separated islands of mucinous maternal



MEDIUM 9-20

- Detail of mucinous lakes containing epithelial elements



HIGH 9-21

- Abnormal collections of epithelial cells with internal lumina

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7. Ramos D, Monteagudo C, Carda C, et al. Clear cell syringoid carcinoma: an ultrastructural and immunohistochemical study. Am J Dermatopathol. 2000;22:60–4.
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Merkel Cell Carcinoma

10

Michael B. Morgan

EPIDEMIOLOGY: Uncommon, elderly with equal gender distribution.
ETIOLOGY: Ultraviolet light, immunosupression, polyoma virus.
PATHOLOGY: Diffuse, trabecular, or nodular aggregates of small blue cells with scant cytoplasm.
PROGNOSIS: Poor, 5-year 50% mortality adverse outcome with lymph node or systemic spread.

Merkel cell carcinoma, otherwise referred to as a trabecular carcinoma, is an uncommon yet deadly dermal neoplasm potentially confused with other cutaneous neoplasms. Like its more common cancerous counterparts in the skin, it most commonly occurs in the sun-exposed sites of elderly patients and is predisposed for by ionizing radiation as well as waning immunity. Its histogenesis is speculated to derive from the slow-adapting dermal neuroendocrine mechanoreceptor known as the merkel cell. The pathology is varied consisting of one or more of three histologic archetypes: (1.) diffuse permeation of the dermis, (2.) large rectangular-shaped trabeculae or as (3.) rounded discrete foci. The latter tumoral disposition is most apt to be confused by the non cognezetti as basal cell carcinoma. The cellular constituency consists of a uniform population of closely opposed cells with scanty cytoplasm and nuclei with indistinct nucleoli. Subtle histologic features that should allow for its distinction in most cases entail: (1.) lack of peripheral tumoral palisading, (2.) lack of tumor-stromal clefting; (3.) increased numbers of mitoses and apoptotic nuclei; (4.) a diffuse nuclear chromatin pattern; (5.) cellular apposition or molding (6.) the presence of tumoral crush artifact. Immunostaining is a useful diagnostic adjunct with particular emphasis placed upon the pattern of cytokeratin immunostaining (dot-like with merkel cell, diffuse in the other carcinomas), neuroendocrine differentiation (synaptophysin, chromogranin positivity) and the absence of lymphoid markers (i.e, CD-45 seen in lymphomas) or lung markers (thyroid transcription factor for metastatic oat cell carcinoma). It should be emphasized that the diagnosis of MCC can be subtle, necessitating its distinction with permanent sections biopsy prior to contemplated frozen section removal. The clinical presentation of these neoplasms is non descript, mimicking other carcinomas including basal cell and squamous cell carcinomas. The biologic course of these neoplasms is extremely aggressive with a propensity to locally recur and to metastasize through a hematogenous or lymphatic route. The overall mortality rate is 50% at 5-years with the most important prognosticators being tumor stage at the time of diagnosis, including the absence of lymph node metastases or evidence of systemic disease. The treatment involves excisional therapy for localized disease and combinations of radiotherapy and chemotherapy for systemic disease. The most effective mode of treatment for localized disease is contentious. Given the aggressive nature of the disease with priority given to its extirpation in lieu of tissue preservation, the subtlety of the tumor cells at the margins or fringe of the tumors and the limitations imposed by the frozen technique, a compelling argument can be marshaled against treating these neoplasms with frozen section margin control or Mohs surgery. However, the cosmetically sensitive locale of these tumors and successful experience in regards to the management of Merkel cell carcinoma with the Mohs technique offer a contravening view. These antithetical views may be reconciled by a practical compromise encompassing the Mohs technique for the initial removal of the tumor followed with a final layer of tissue submitted for permanent section evaluation.

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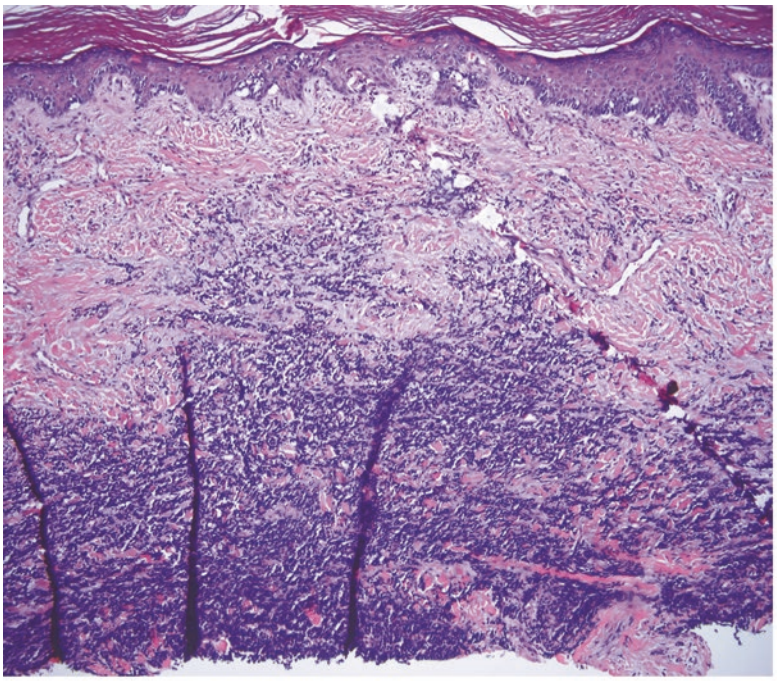
M. B. Morgan et al. (eds.), *Atlas of Mohs and Frozen Section Cutaneous Pathology*,
https://doi.org/10.1007/978-3-319-74847-4_10

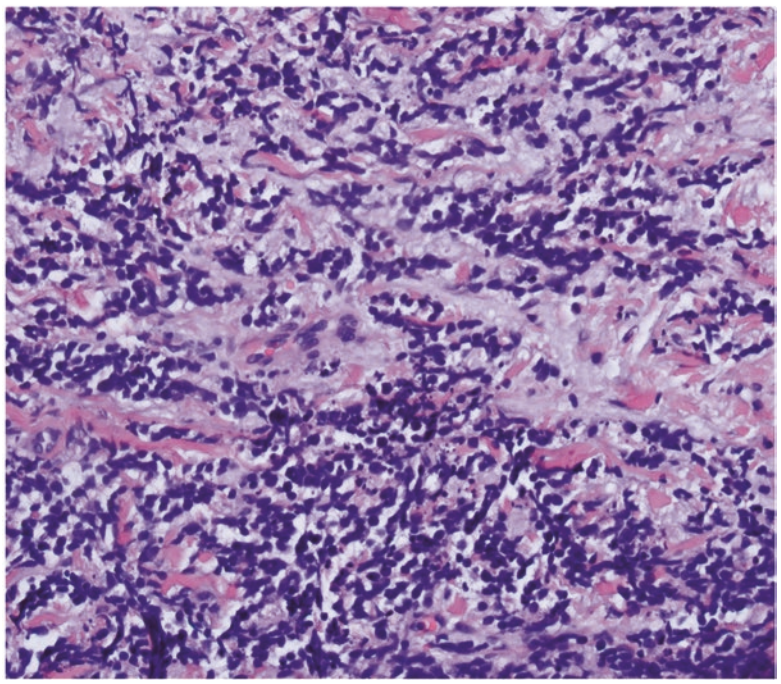
Merkel Cell Carcinoma–Diffuse Pattern



LOW 10-1

- Intraepidermal and diffuse dermal neoplasm

Note: Tumor density increases with dermal descent

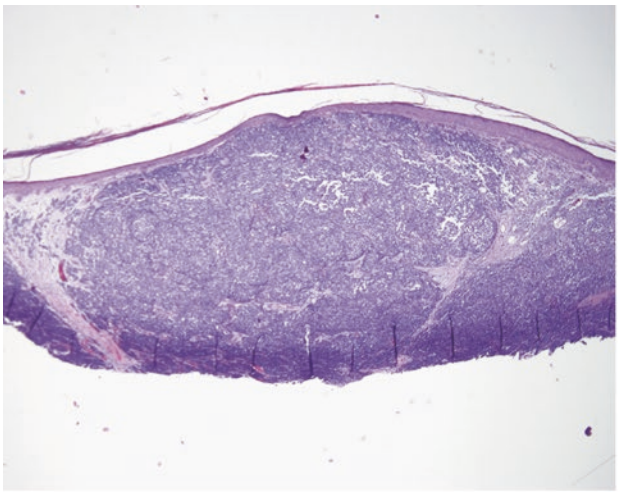


HIGH 10-2

- Diffuse permeation between dermal collagen bundles

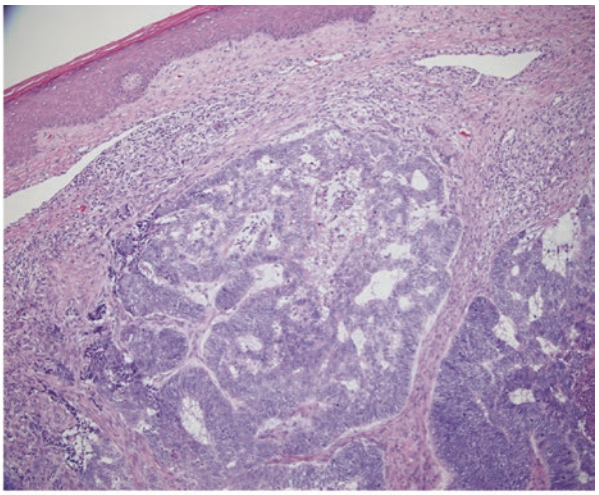
Note: Scanty cytoplasm with nuclear apposition

Merkel Cell Carcinoma–Trabecular Pattern



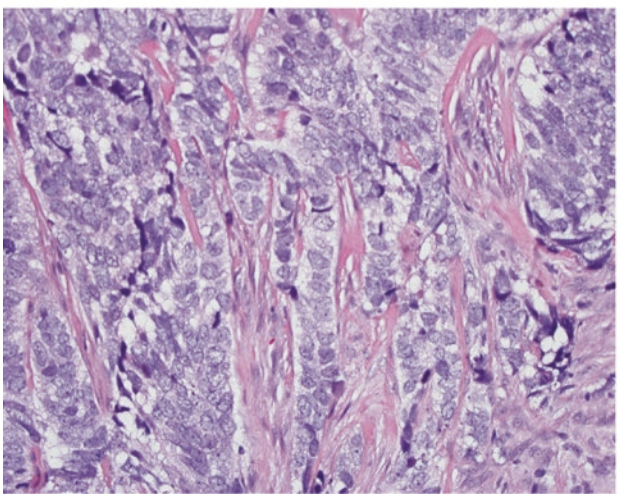
10-3

- Expansive dermal neoplasm



10-4

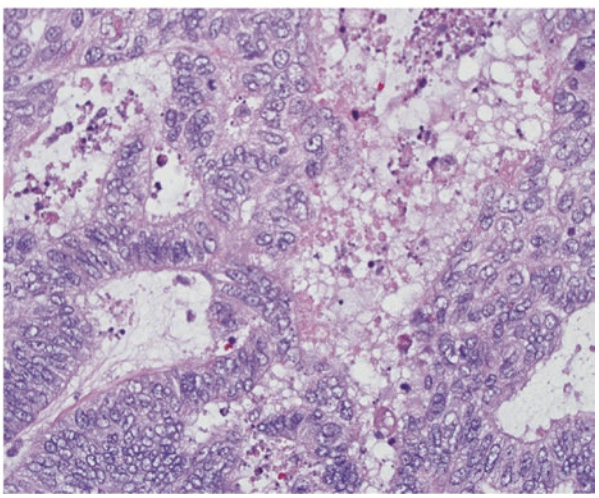
- Neoplasm comprised of trabeculae



10-5

- Rectangular configured trabeculae

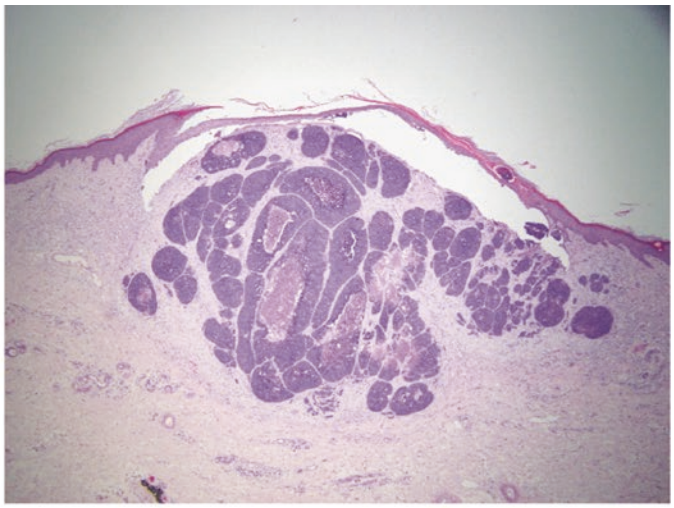
Note: Open nuclear chromatin patterns



10-6

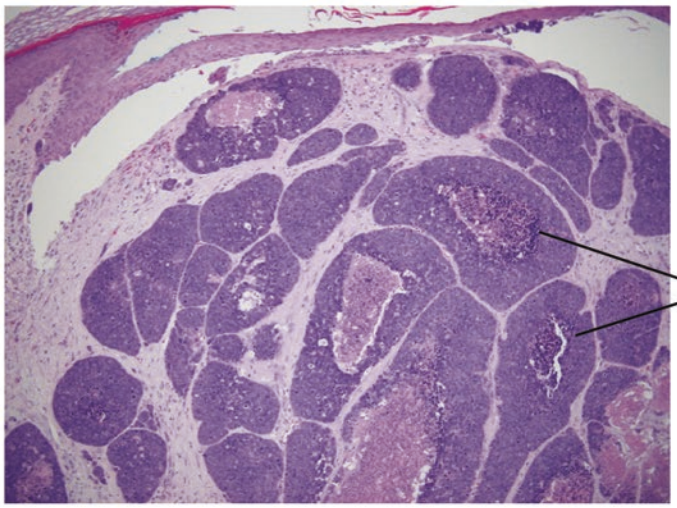
- Trabeculae showing increased numbers of mitosis and apoptotic figures

Merkel Cell Carcinoma–Nodular Pattern



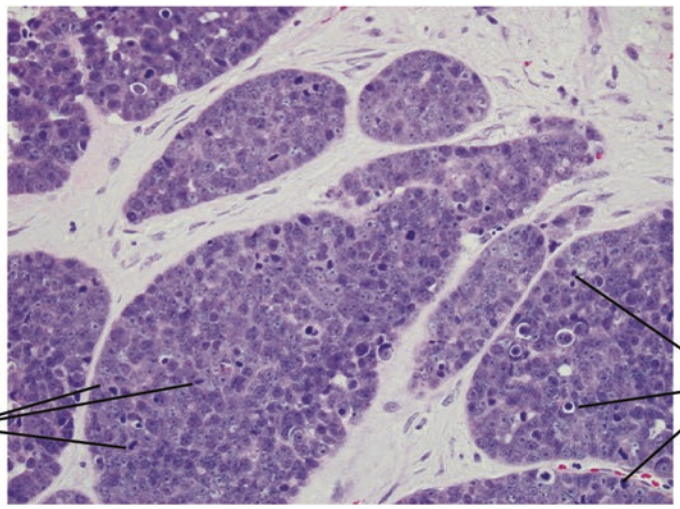
- Asymmetric dermal nodular proliferation

10-7



- Basaloid nodule showing central necrosis

10-8



- Cytologic detail

  Note: Absence of palisading, increased numbers of mitosis and apoptotic figures

10-9

Bibliography

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Sebaceous Tumors

11

Michael B. Morgan

EPIDEMIOLOGY: Uncommon, approximately 1/2 occur on eyelids, elderly with equal gender, syndromic females are at a younger age.
PATHOGENESIS: Derive from Meibomian glands, other sebaceous glands, assoc. with XRT and Muir-Torre Syndrome.
PATHOLOGY: Pagetoid or invasive basaloid or squamous cells with sebocytic cells showing clear cytoplasmic vacuoles.
CLINICAL: Non-descript ulcerating papule, may be yellow in appearance or involve both eyelids.
PROGNOSIS: Poor with 25% patients with metastatic disease at diagnosis with 50% 5-year mortality, lymph nodes.

Sebaceous carcinoma, otherwise referred to as meibomian gland carcinoma, is an uncommon-yet-aggressive sebaceous neoplasm that occurs within the eyelid. Although histologically identical tumors may occur within any sebaceous gland containing a cutaneous site, they do not pursue as an aggressive biologic course and, given their less sensitive anatomic location, may not require the use of tissue sparing frozen section/Mohs resection treatment. The meibomian glands are modified sebaceous glands devoid of an interposed follicle found in association with the upper and lower tarsal eyelid plates. These glands are distinct from the eyelash-associated sebaceous glands of Zeis or similar glands associated with caruncle or surface vellus hairs. The pathogenesis of these neoplasms is unknown although ultraviolet and ionizing irradiation have been implicated in their development. Sebaceous carcinoma is also associated with the Muir-Torre DNA-mistmatch repair defect syndrome. Unlike sporadic cases seen in the elderly, those tumors that arise in conjunction with this syndrome tend to afflict the middle-aged patient. The microscopic features are distinct and consist of the demonstrated presence of sebocytic differentiation. The latter change consists of neoplastic cells possessing enlarged nuclei with prominent nucleoli and most importantly, lipid cytoplasmic vacuoles that appear as multiple rounded clear areas or as diagnostic areas of staining with lipid stains on fresh frozen biopsy tissue specimens. Fat staining with agents such as Oil red-O cannot be performed on formalin fixed or processed tissues. Instead, the diagnosis relies upon the demonstration of the sebocytes or of sebaceous differentiation with the aid of immunohistochemical staining. The latter technique can be employed on frozen or formalin-fixed tissues and consists of epithelial membrane antigen (EMA) or carcinoembryonic antigen (CEA) or cytokeratin -7 (CK-7) immunopositivity. These immunostains

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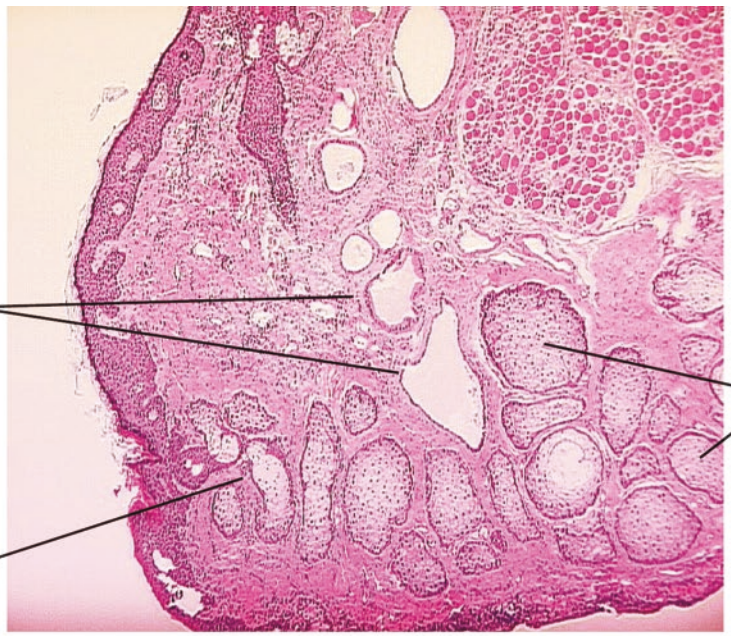
https://doi.org/10.1007/978-3-319-74847-4_11

should not decorate the cells comprising routine squamous cell or basal cell malignancies. Exceptionally, sebaceous carcinoma may present in the histologic guise of basal cell carcinoma or squamous cell carcinoma showing only focal sebocytic differentiation. This histologic continuum can pose significant quandry on the eyelid where sebaceous carcinoma pursues a more aggressive course. Sebaceous carcinoma typically presents as invasive infiltrative neoplasm or rarely as an intraepidermal neoplasm showing pagetoid spread simulating Bowen's or Paget's disease. The clinical appearance of these lesions is non descript, being similar to their more common basal cell or squamous cell counterparts. Approximately 25% of tumors will have metastasized to regional lymph nodes at the time of diagnosis. The prognosis of patients with metastatic disease drops to 50% at 5 years.

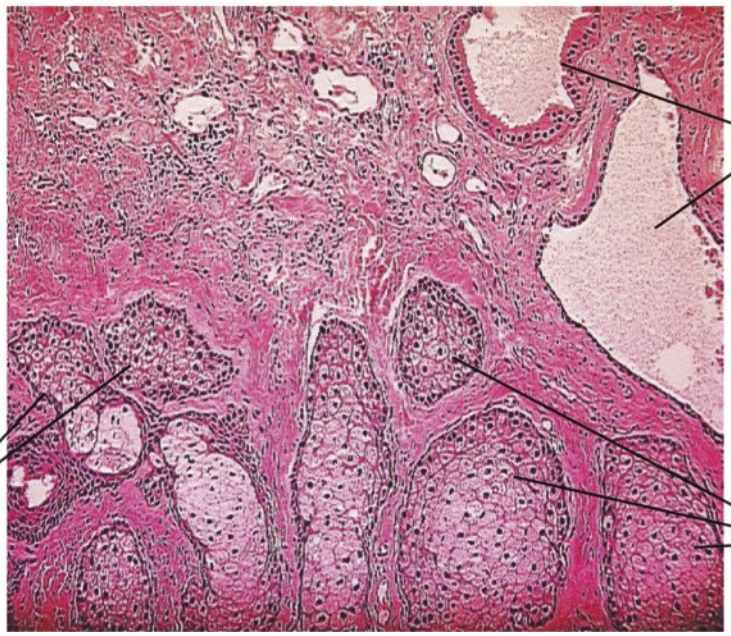
Normal Eyelid Anatomy



- Lobed structure with epithelium circumferentially surrounding specimen

Note: Bundles of skeletal muscle and sebaceous lobules

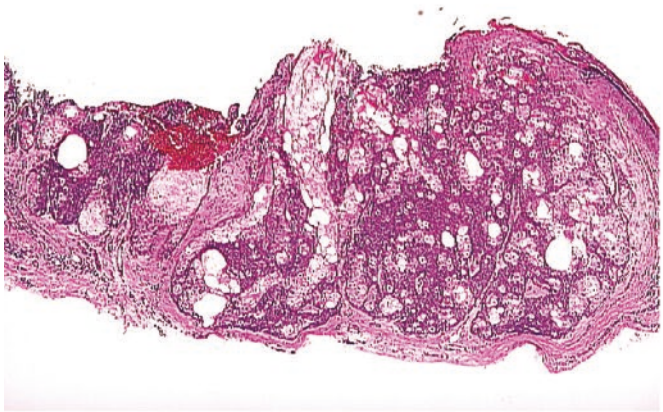
LOW 11-1



- Detail of zeis and meibomian glands

HIGH 11-2

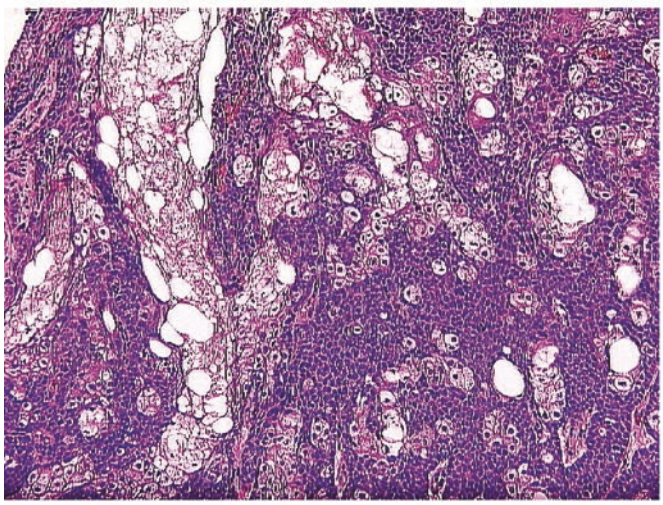
Sebaceous Adenoma



11-3

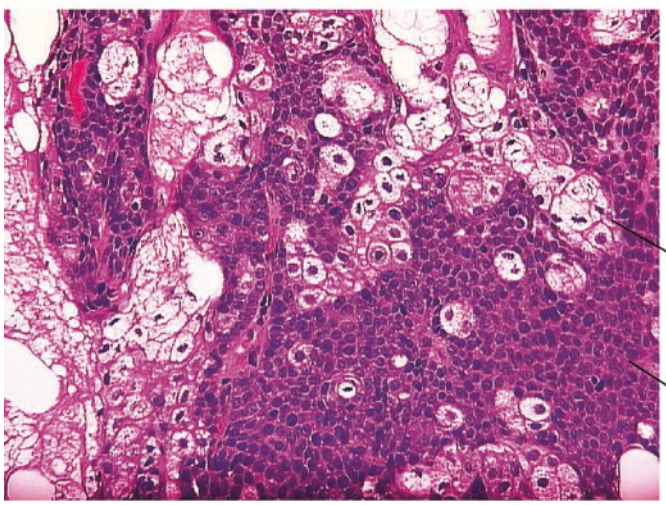
- Low power detail of sebaceous adenoma

Note: Circumscription of the tumor and proximity to the epithelium



11-4

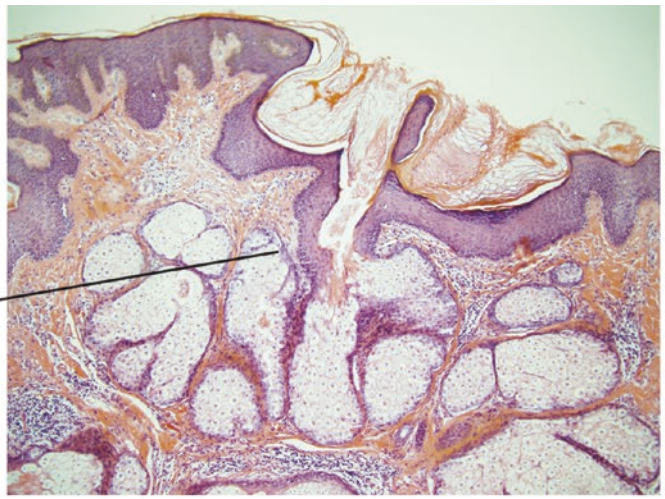
- Detail of cellular composition with admixture of basaloid primordial cells and clear sebocytes



11-5

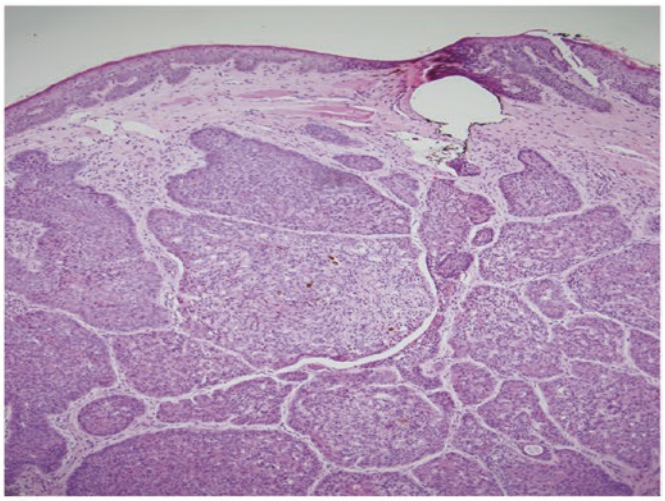
Note: The near equal number of clear sebocytes and basaloid germinative cells

Benign Sebaceous Tumors



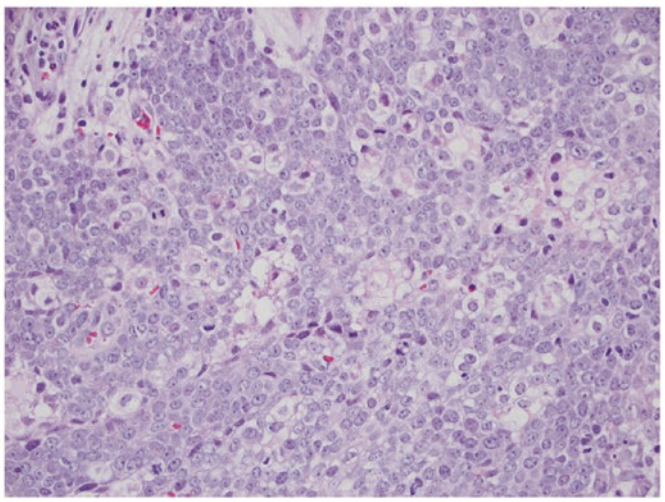
SEBACEOUS HYPERPLASIA 11-6

- Hypertrophied mature sebaceous lobules emanating from central follicle



SEBACEOUS EPITHELIOMA *LOW* 11-7

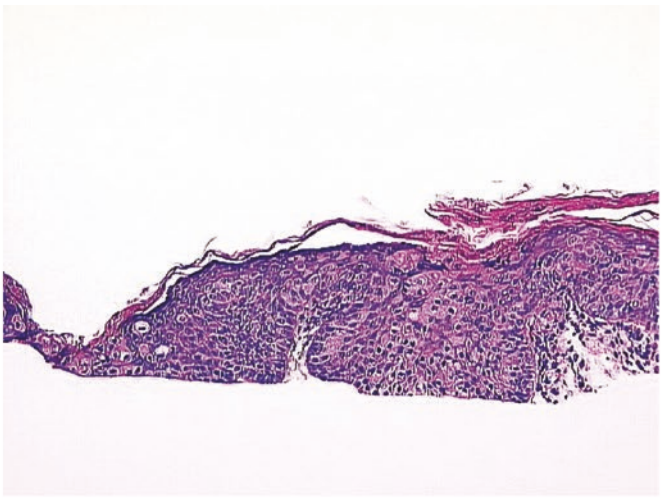
- Irregular basaloid tumoral foci occupying the dermis



SEBACEOUS EPITHELIOMA *HIGH* 11-8

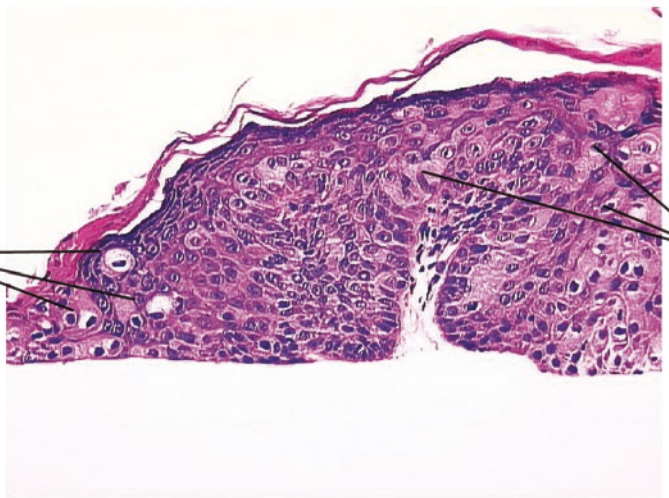
- Clear cells within tumoral foci corresponding to sebocytic differentiation

Intraepidermal Sebaceous Carcinoma



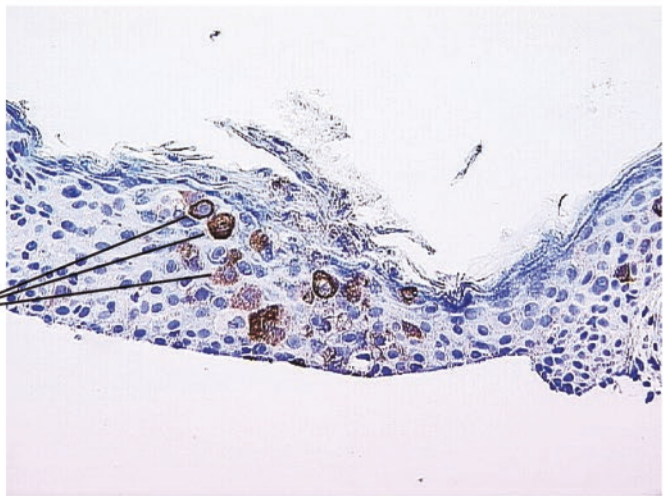
- Neoplastic cells confined to the epithelium
- Prognosis similar to conventional SCC-in-situ

LOW 11-9



- Pagetoid scatter of clear cells

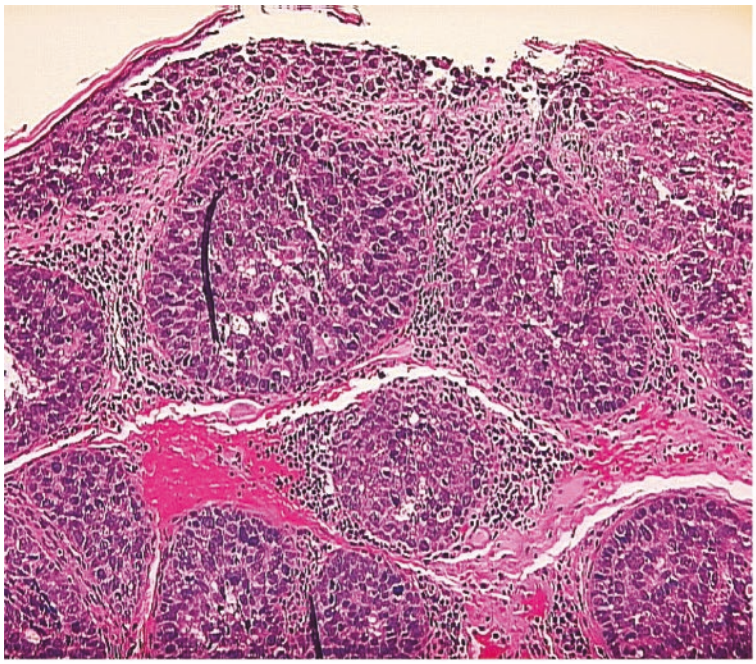
HIGH 11-10



- CK-7 immunostain highlighting pagetoid scatter of abnormal cells

CK-7 11-11

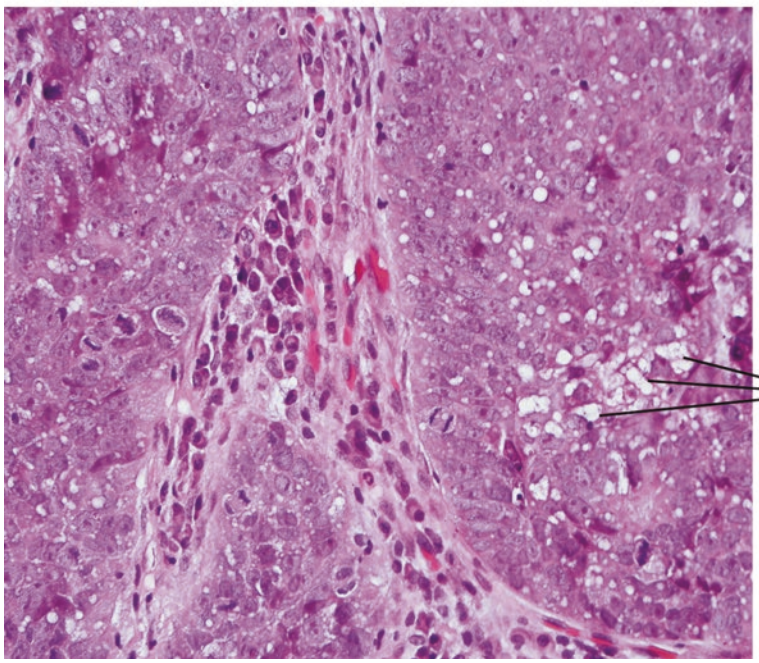
Sebaceous Carcinoma-Invasive



- Invasive dermal neoplasm

Note: Intraepidermal component

LOW 11-12



- Basaloid tumoral foci containing vacuolated clear cells

HIGH 11-13

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Paget's Disease

12

Michael B. Morgan

EPIDEMIOLOGY: Uncommon, elderly, mammary and extra-mammary.
ETIOLOGY: Unknown
PATHOLOGY: Single and nested clear cells throughout the epithelium, CEA+, CK-7+, EMA+.
CLINICAL: Scaly or erythematous patch areola or genitalia.
TREATMENT: Supportive for mammary, excision with genitourinary/gastrointestinal w/u for extra-mammary.

Cutaneous Paget's disease may be an important harbinger of an underlying visceral malignancy. The most important forms of Paget's disease entail a genital or extra-mammary form imbued with a tenuous association with underlying genitourinary or gastrointestinal adenocarcinoma and a mammary form of the disease that connotes an inevitable association with underlying breast adenocarcinoma. Both forms represent the intra-epithelial proliferation of glandular-derived malignant cells. These cells derive from the adnexal or adnexal-like apocrine or sebaceous glands of their respective anatomic structures. The pathogenic mechanisms or etiology of these diseases remain unknown as does the exact pathogenic relationship that these tumors potentially possess with their respective underlying malignancies. The clinical presentation involves a scaly patch of the breast nipple or an erythematous patch of the genitalia. The pathology is typically configured as a confluent and randomly scattered spread of abnormal polygonal-shaped clear cells throughout the epithelium. The confluent foci tend to be seen in basilar portions of the epithelium with some tendency of these cells to coalesce forming glandular foci with central lumina seen. The cells themselves possess ample amounts of foamy-to-clear cytoplasm with occasional vacuoles. The nuclei are enlarged and possess prominent central nucleoli. These cells sometimes referred to as Paget cells, are typically carcinoembryonic antigen (CEA), cytokeratin-7, epithelial membrane antigen positive and cytokeratin-20, high molecular weight keratin, S-100 and leukocyte common antigen (LCA) negative on immunohistochemical staining. The latter stains are important to examine as the most important entities that can masquerade as Paget's disease and entail the pagetoid scatter of atypical intraepidermal cells include CK-20 merkel cells, high molecular weight keratin squamous cell carcinoma cells, S-100 melanoma cells and LCA lymphoma cells. The prognosis of mammary Paget's disease remains guarded and, given its inviolate association with underlying breast adenocarcinoma, is treated with local surgery often entailing mastectomy with adjuvant radiotherapy and chemotherapy. Genital forms of the disease portend a significantly better prognosis with approximately 20% associated with underlying cervical, bladder, prostate or colorectal adenocarcinoma. The cutaneous expression of the disease even among patients with demonstrated visceral involvement, can be successfully treated with frozen-section-aided excisional or Mohs micrographic surgery.

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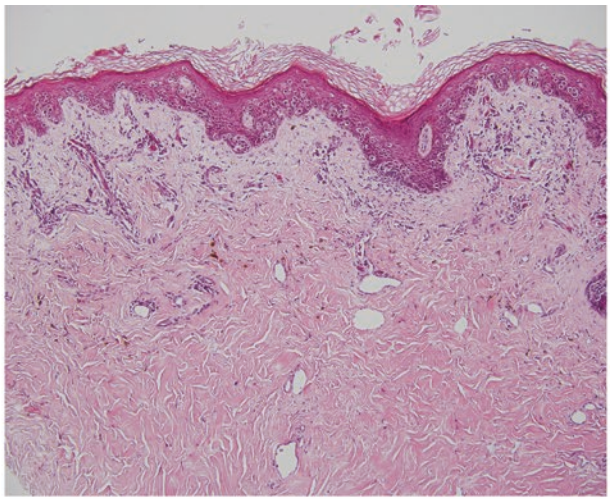
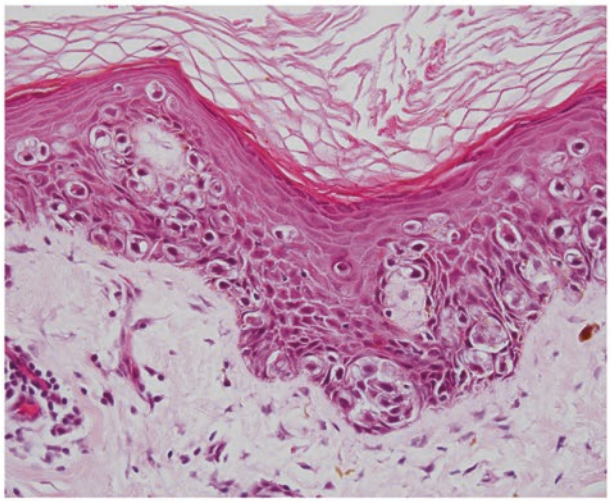
M. B. Morgan et al. (eds.), *Atlas of Mohs and Frozen Section Cutaneous Pathology*,
https://doi.org/10.1007/978-3-319-74847-4_12

Paget's Disease



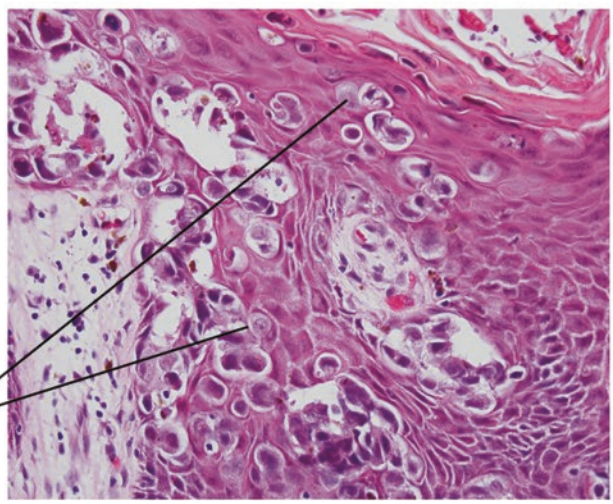
12-1

- Wide spread clear cell scatter throughout all levels of the epithelium



12-2

- Nested and singly arrayed pagetoid clear cells



12-3

- Detail of Paget's cells

Note: Prominent nucleoli

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Melanocyte Pathology

13

Michael B. Morgan

EPIDEMIOLOGY: Common, 1/20 incidence of basal cell carcinoma.
PATHOGENISIS: UV light, p-53, C- kit, p16 Braf/ras/erk genetic defects.
CLINICAL: Irregular hyperpigmented patch on sun-exposed site.

In the examination of melanocytes by frozen section pathology, sub-optimal preservation, freeze artifact, overlapping histologic criteria between melanocytes and confusion with other resident epidermal cells may all conspire to render the evaluation of these lesions problematic. For these reasons as well as the practical concerns of jurisprudence and affording the best technique for the evaluation and treatment of these neoplasms, discussion will be limited to the adjudication of incidental nevocellular nevi and melanoma-in-situ. It is the opinion of this author (M.B. Morgan, M.D.) that dysplastic or other atypical nevi including Spitz nevi and invasive melanoma are best assessed through traditional histological techniques and that the treatment of invasive melanoma should concern wide local margin excision with permanent section margin assessment. Incidental nevocellular dermal aggregates are commonly encountered in the examination of frozen sections of cutaneous neoplasms. The nevic rests can be seen anywhere within the dermis particularly in perifollicular locales. The nevi themselves typically form loose clusters and are composed of a uniform population of rounded cells with scant eosinophilic cytoplasm containing rare melanin pigment. The nuclei are typically round and may contain cytoplasmic pseudo-nuclear inclusions. Melanoma-in-situ is most commonly encountered in the setting of chronic actinic damage on the head and neck or exposed extremities clinically configured as the Hutchinson's freckle or lentigo-maligna. The melanocytes composing these lesions may be configured as subtle haloed-single cells along the dermo-epidermal junction or entail inter-follicular skip areas with transfollicular extension. Classic criteria of melanoma-in-situ consisting of melanocyte nesting along the dermo-epidermal junction, contiguous basilar layer proliferation and pagetoid scatter should be sought after as important features of these neoplasms. Among the more difficult tasks for the microscopist is the discernment of individual atypical melanocytes in conjunction with solar-induced hyperplasia/hypertrophy and their distinction from other resident cells that possess similar cytologic features. While the average of 1 melanocyte per 10 keratinocytes may exceed a numerical factor of 1 melanocyte per 5 keratinocytes in sun-damaged cutaneous sites such as the face, melanocyte numbers exceeding this ratio, situated as contiguous runs of two or more adjacent melanocytes or showing interfolliclar extension should be regarded as suspicious for melanoma-in-situ. Although Langerhans cells and Merkel cells can be seen along the dermoepidermal junction and can possess pericellular halos as observed with melanocytes, they typically exist in lower numbers on the face or in areas that have received excessive ultraviolet exposure. Another pitfall concerning the histologic assessment of abnormal melanocytes regards the occasional upward displacement or pagetoid scatter of melanocytes with acute ultraviolet exposure, friction as typically observed within intertriginous sites or in concert with repair in the setting of scars. Situations that

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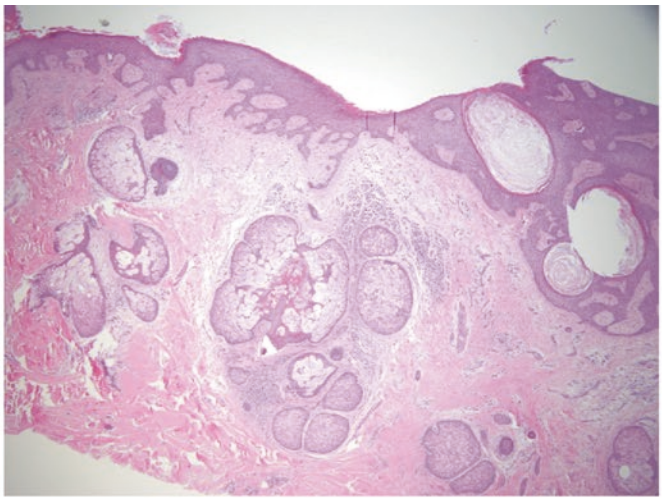
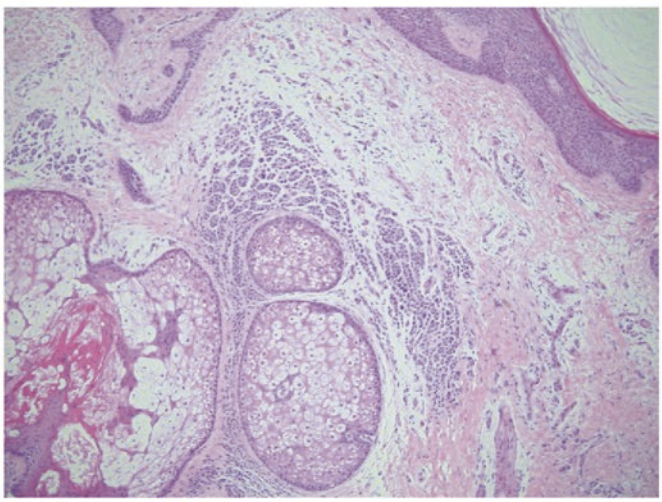
entail such aforementioned scenarios should prompt appropriate caution and mandate conservative histologic assessment. The application of imunohiostochemical stains such as S-100 or melan-A to the adjudication of these lesions is fraught with technical and practical concerns. Technical considerations notwithstanding, the histologic assessment of S-100 positive cells is limited due to its lack of specificity with similar staining dendritic Langerhans cells and with melan-A due to the non-specific staining of melanosome-containing melan-A positive keratinocytes. The immunohistochemical application to melanocytic lesions will be subsequently discussed in a forthcoming chapter.

Intradermal Nevus



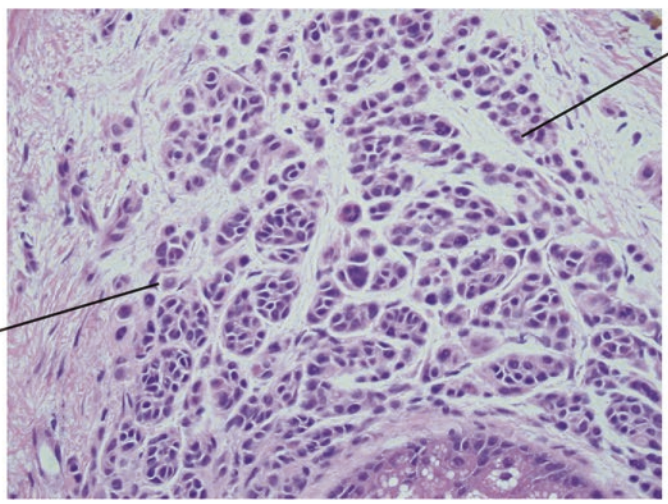
LOW 13-1

- Subtle well-circumscribed nevocellular nests seen near follicle



MEDIUM 13-2

Note: Subtle nesting pattern

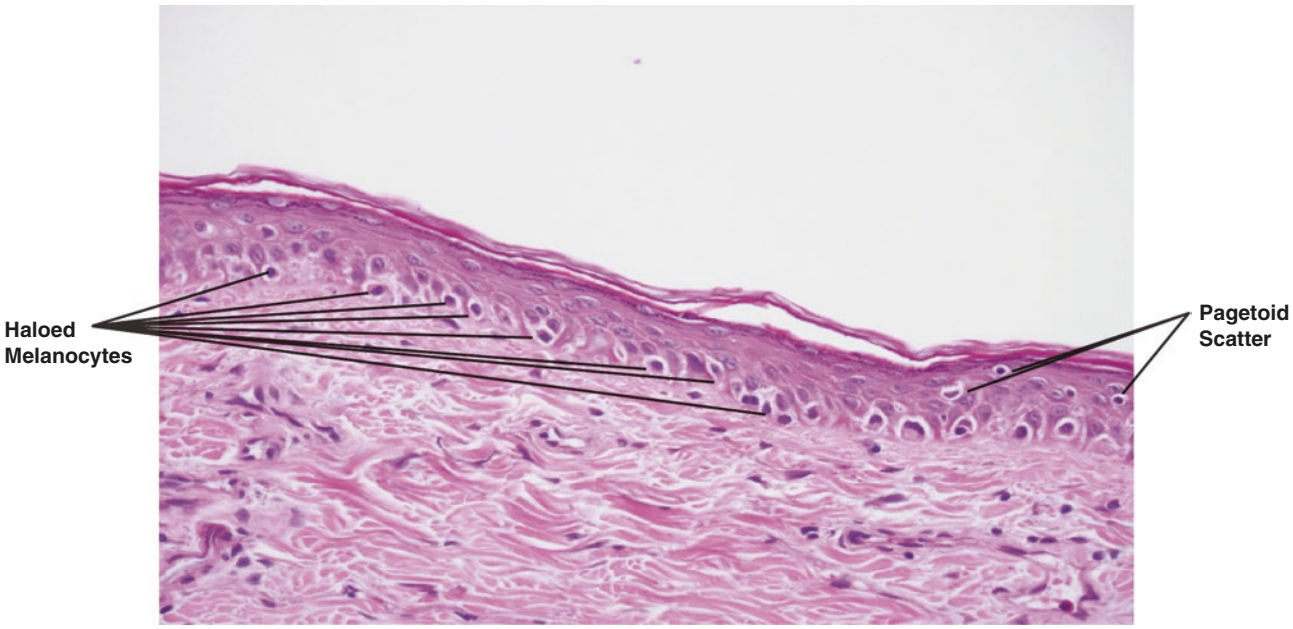


HIGH 13-3

- Nested nevocellular cells

Note: Scattered cytoplasmic nuclear inclusions

Atypical Melanocytic Hyperplasia/Subtle MIS



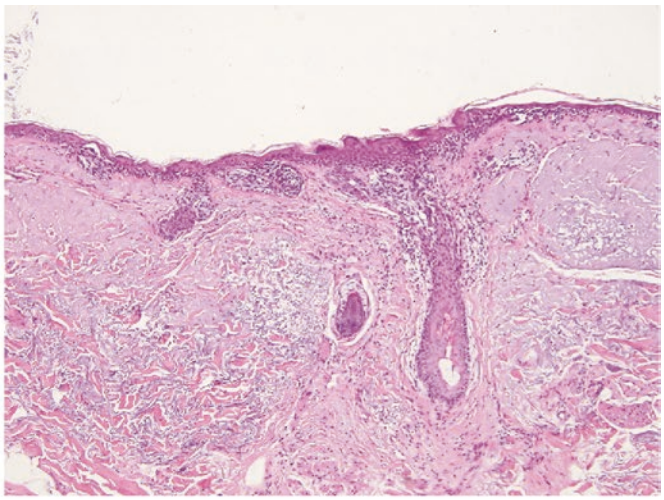
13-4

- Increased numbers of atypical (enlarged) melanocytes

Note: ≥2 melanocytes/5 basilar keratinocytes

Note: Pagetoid (upward) scatter of melanocytes

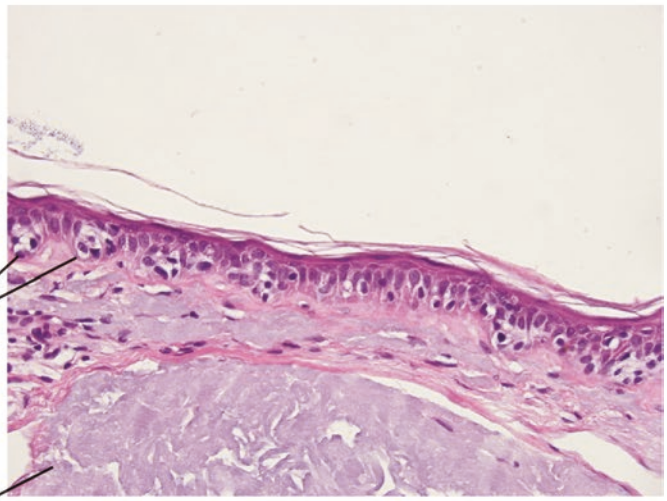
Melanoma-in-Situ



LOW 13-5

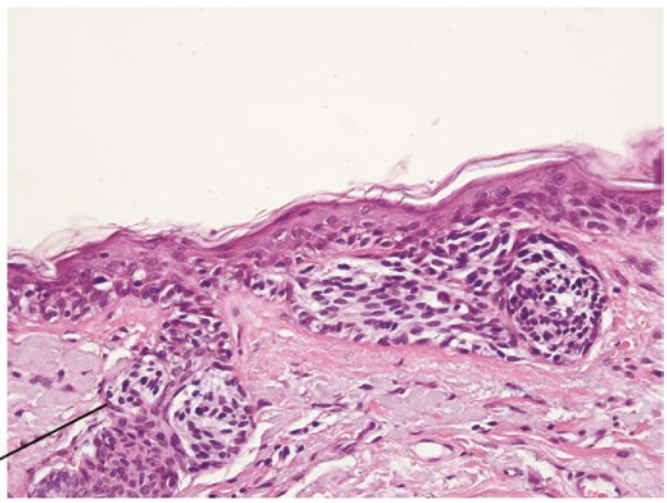
- Irregular nesting pattern of melanoma cells

Note: How nests vary in size and distribution



MEDIUM 13-6

- Increased numbers of nested and singly arrayed melanocytes



HIGH 13-7

- Detail of nests

Note: Irregularity of nests

Note: Follicular extension of nests

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Part III

Tumors of the Dermis

Benign Mesenchymal Tumors

14

Michael B. Morgan

The mesenchymal tumors are derived from mesodermally-derived tissues native to the dermis and include fibrous, vascular, adipose and neural neoplasms. As these lesions may rarely be confused with their malignant counterparts, attention will be given to their elucidation.

Dermal mesenchymal tumors are collectively common and encompass the gamut of benign mesodermally-derived tumors that recapitulate their respective native tissues endogenous to the cutaneous dermis and subcutaneous fat. The most important task a pathologist has is to differentiate them from their malignant counterparts.

The most important fibrous tumors include dermatofibroma derived from the native dermal dendrocyte capable of being confused with dermatofibrosarcoma protuberans. Attention should be placed upon the presence of a grenz-zone, looser texture, collagen trapping and lack of subcutaneous fat permeation in dermatofibroma compared to dermatofibrosarcoma protuberans. Fibrous papule is a common histologically-distinct neoplasm usually encountered in the mid-face region, comprising capillaries and dendritic fibrocytes showing characteristic perifollicular whorling that may be clinically confused with basal cell carcinoma.

The vascular tumors consist of varying proliferations of endothelial-lined vascular spaces that most importantly can be confused with malignant vascular neoplasms such as Kaposi's sarcoma and angiosarcoma. Capillary hemangioma and lobular capillary hemangioma (pyogenic granuloma) may be composed of numerous endothelial cells seen forming poorly delineated vascular spaces potentially confused with malignant vascular tumors. However, attention should be given to their circumscription within the dermis, absence of tumor cell spindling or the formation of anastomosing vascular spaces as encountered in Kaposi's sarcoma or angiosarcoma, respectively. Angiokeratoma is a benign vascular neoplasm comprising well-formed endothelial lined vascular spaces seen in close proximity to the overlying, often acanthotic epidermis. They may be clinically confused with melanoma particularly following spontaneous vascular thrombosis.

The adipose tumors consist of well-circumscribed collections of mature adipose tissue with varying degrees of vascular (angiolipoma) or fibrous (fibrolipoma) tissues typically seen in the subcutaneous fat or rarely, the dermis.

The neural neoplasms consist of benign proliferations of mature nerve sheath tissue. Neurofibroma represents the growth of neural Schwann cell, fibroblast and specialized pernineural fibroblasts in a diffuse pattern. These lesions are often punctuated by mast cells. Schwannoma, otherwise referred to as neurolemomma or its diminutive cousin, palisaded and encapsulatd neuroma, represent pure proliferations of encapsulated Schwann cells often forming cellular (Antoni A) and acellular (Antoni B) zones with a tendency to palisade (Verocay bodies).

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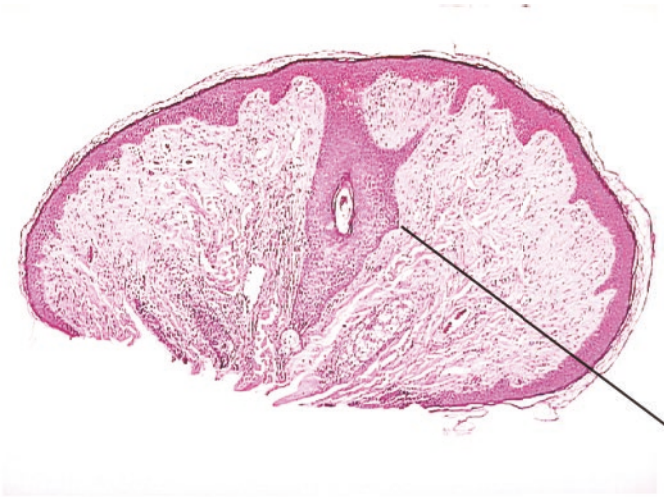
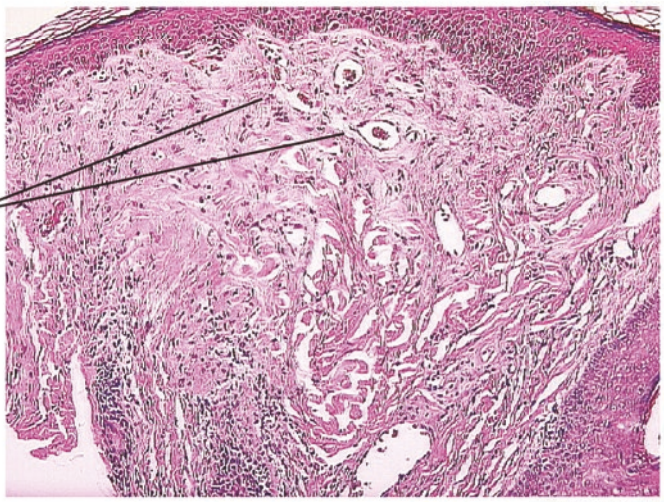
Angiofibroma/Fibrous Papule



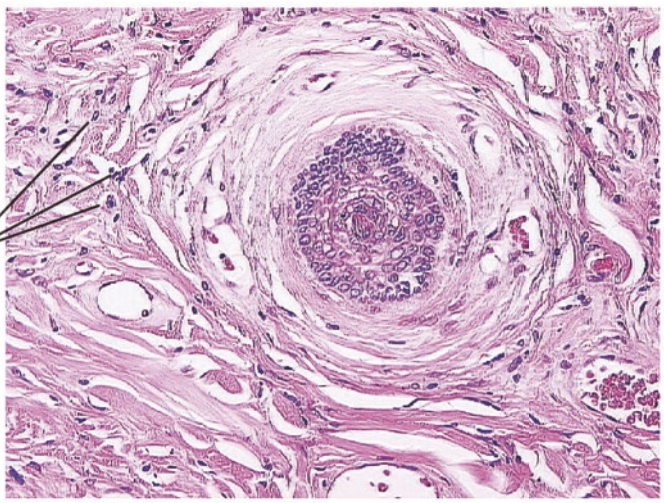
- Dome-shaped papule
- Centered on central follicle

LOW 14-1



- Proliferation of capillaries and interstitial fibrocytes

MEDIUM 14-2

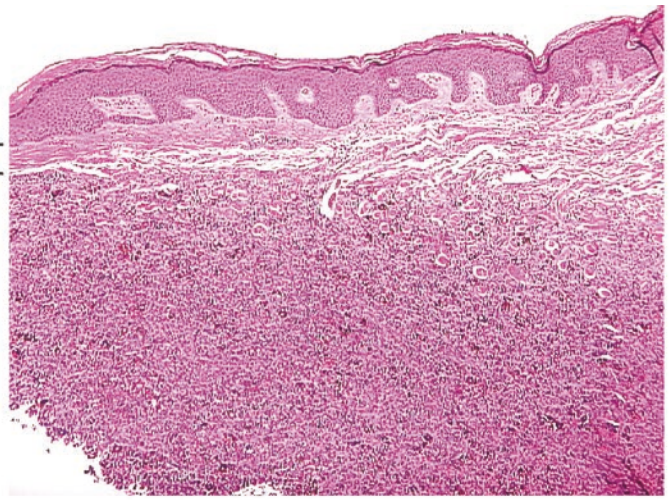


- Characteristic perifollicular whorling of fibrous tissue

Note: Dendritic/stellate fibrocytes

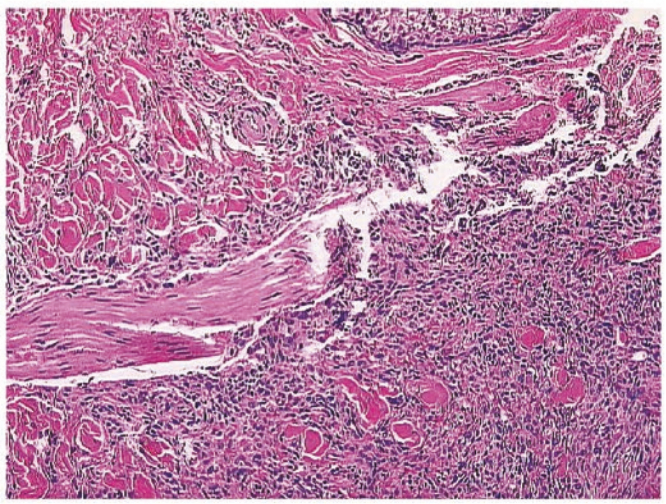
HIGH 14-3

Dermatofibroma



LOW 14-4

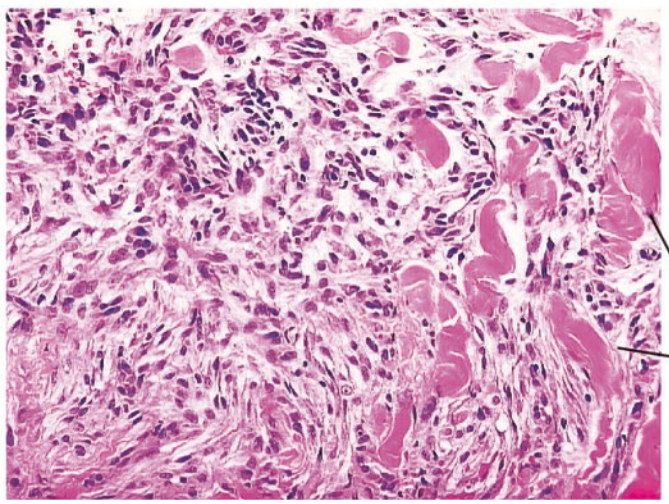
- Acanthotic epithelium
- Grenz Zone
- Dermal spindle cell neoplasm



MEDIUM 14-5

- Interstitial proliferation of spindled cells

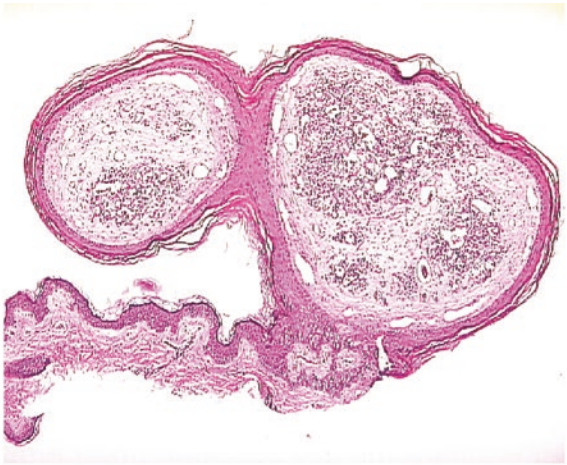
Note: Trapping of collagen fibers



HIGH 14-6

- Hypertrophied collagen fibers
- Tight spindled whorls

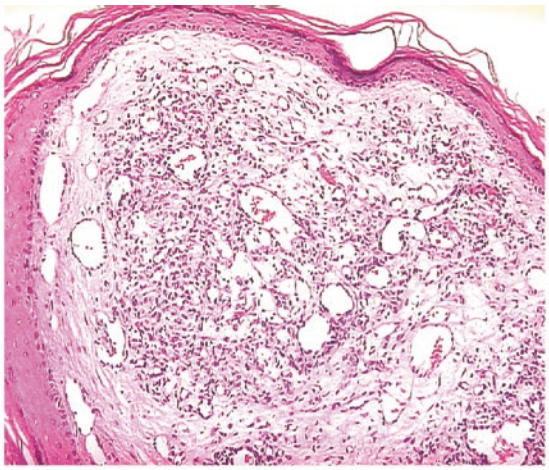
Benign Vascular Tumors



LOBULAR CAPILLARY HEMANGIOMA

LOW 14-7

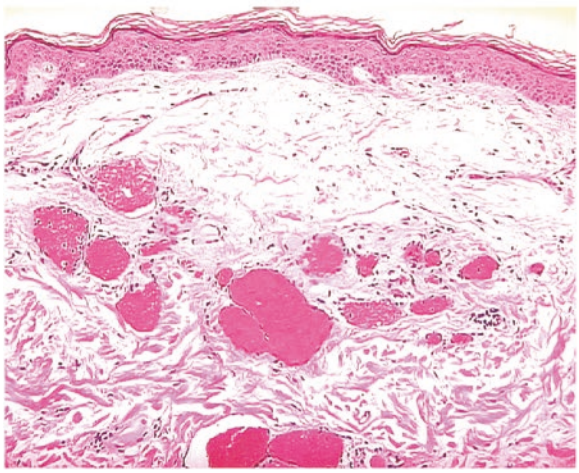
- Exophytic papule
- Circumscribed vascular proliferations



LOBULAR CAPILLARY HEMANGIOMA

HIGH 14-8

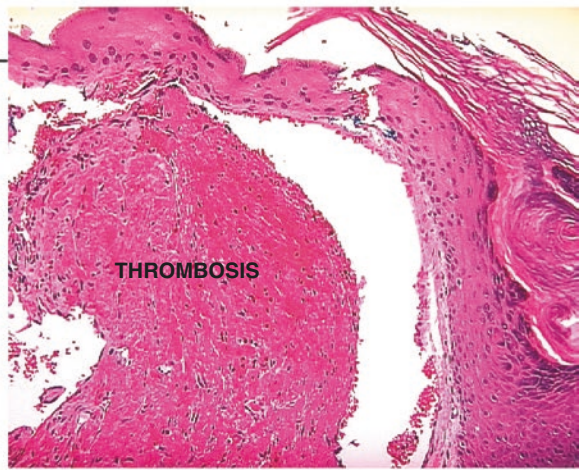
- Dilated and compressed vascular channels
- Extravasated erythrocytes



HEMANGIOMA

14-9

- Dilated circumscribed collection of endothelial-lined blood filled vessels

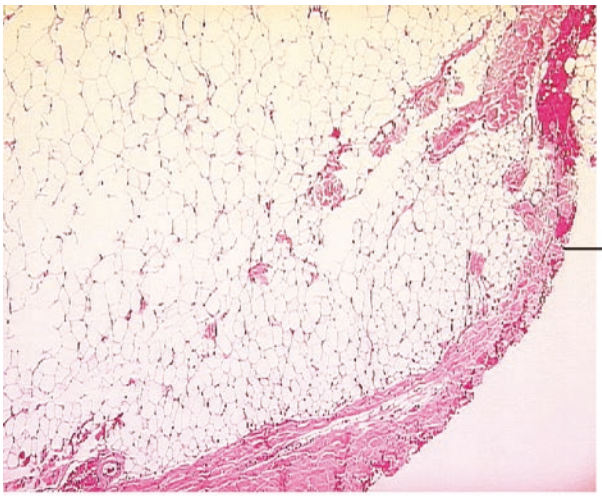


ANGIOKERATOMA

14-10

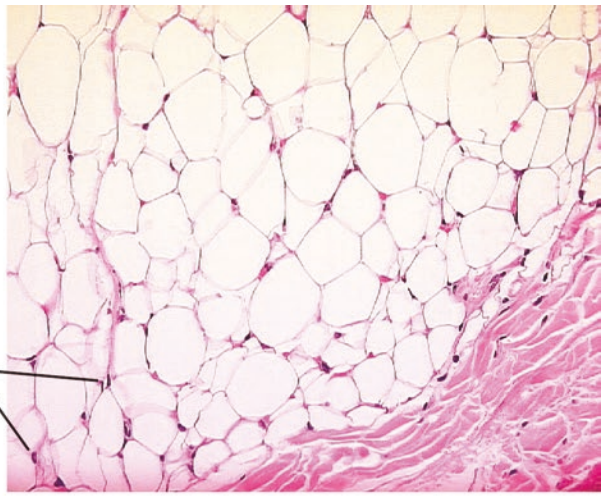
- Endothelial-lined vascular space in close proximity to the epithelium
- Central thrombosis

Lipoma/Angiolipoma



14-11

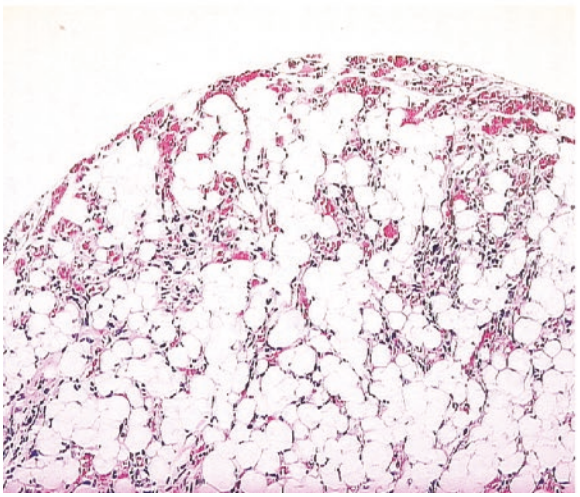
- Well-circumscribed collection of mature adipocytes



14-12

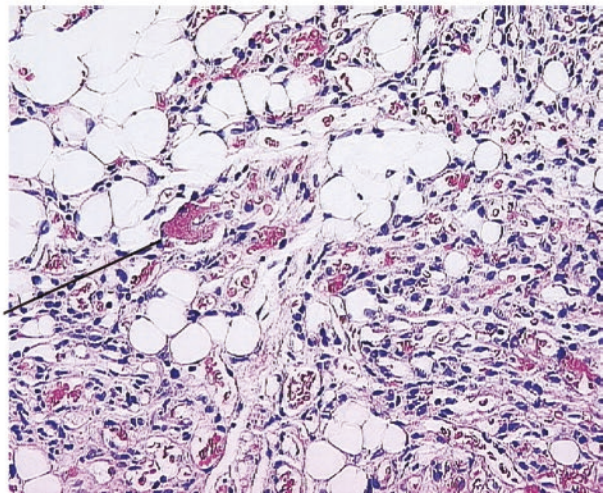
- Detail of adipocytes

Note: Condensed peripheral nuclei



14-13

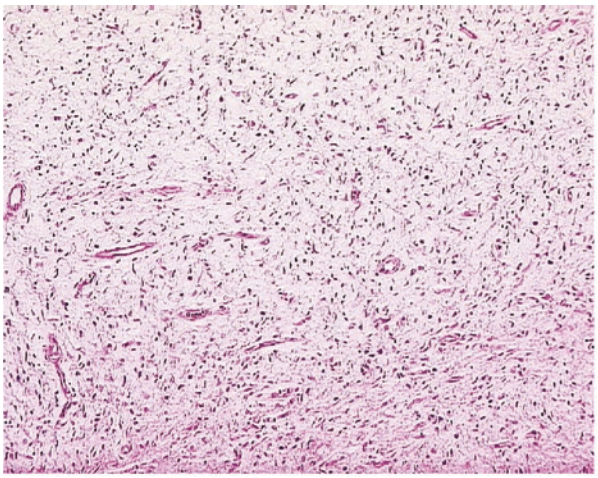
- Admixture of adipocytes and capillaries



14-14

- Capillaries forming dilated and slit-like spaces with vascular thrombosis

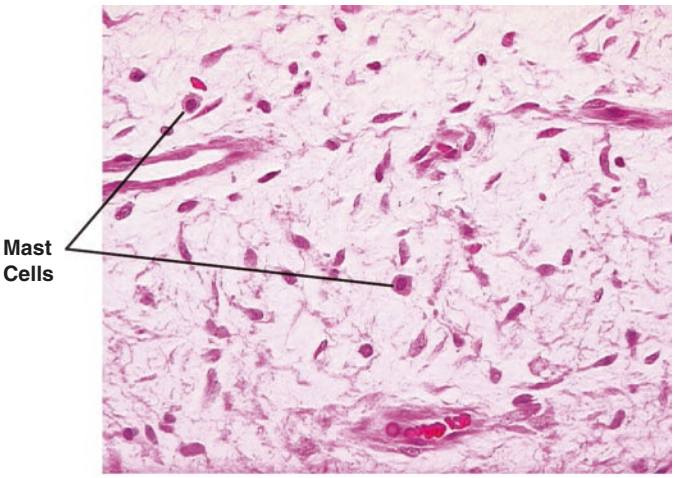
Benign Nerve Sheath Tumors



NEUROFIBROMA *LOW* 14-15

- Loose textured pale neoplasm

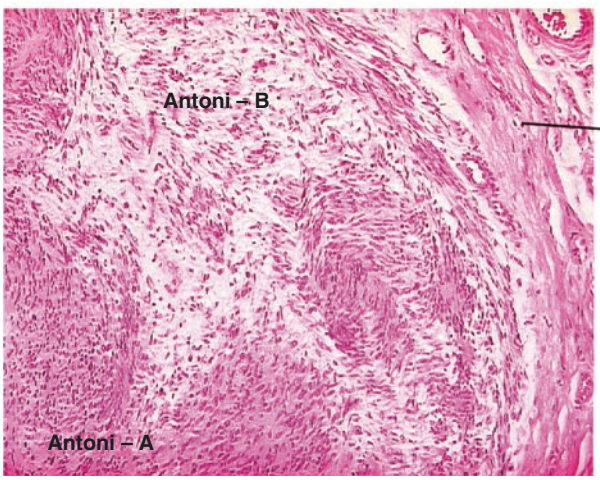
Note: Abundant capillaries



NEUROFIBROMA *HIGH* 14-16

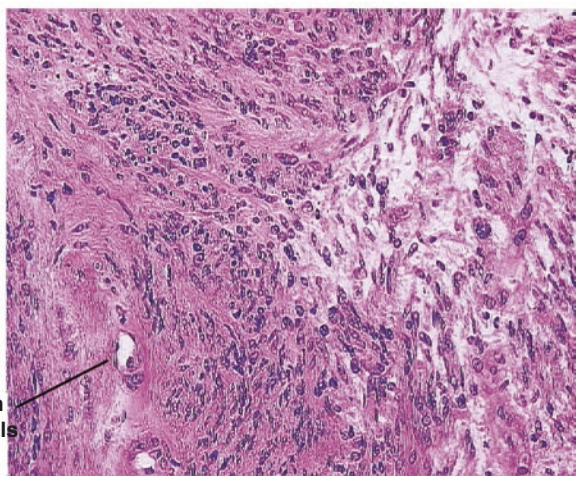
- Prominent capillaries set in paucicellualr myxoid stroma

Note: Scattered fried-egg like mast cells



SCHWANNOMA *LOW* 14-17

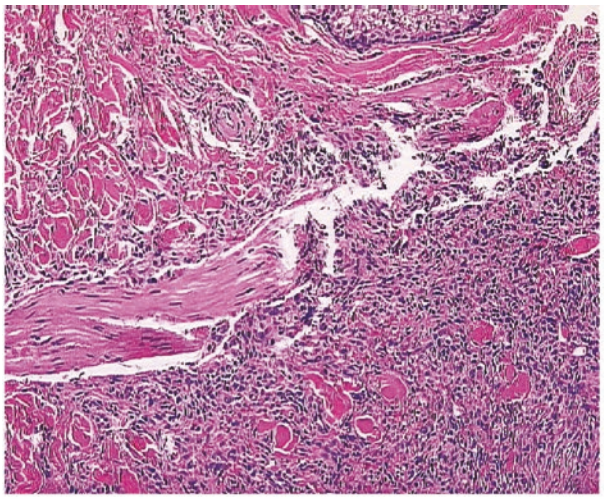
- Biphasic circumscribed spindle cell neoplasm with cellular Antoni-A and acellular Antoni-B foci



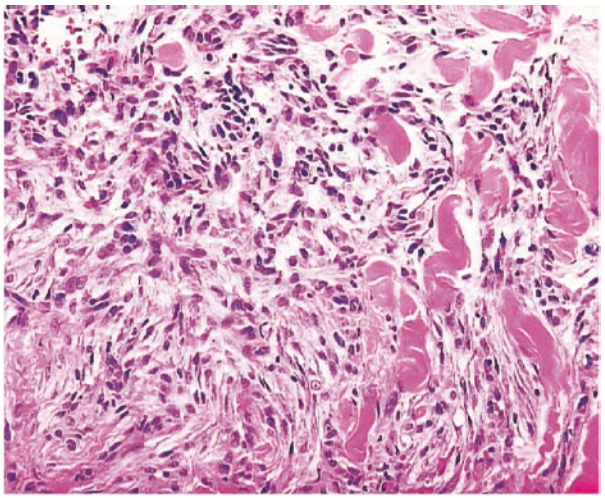
SCHWANNOMA *HIGH* 14-18

- Prominent blood vessels with hyalinization

Challenges
Dermatofibroma / Dermatofibrosarcoma Protuberans

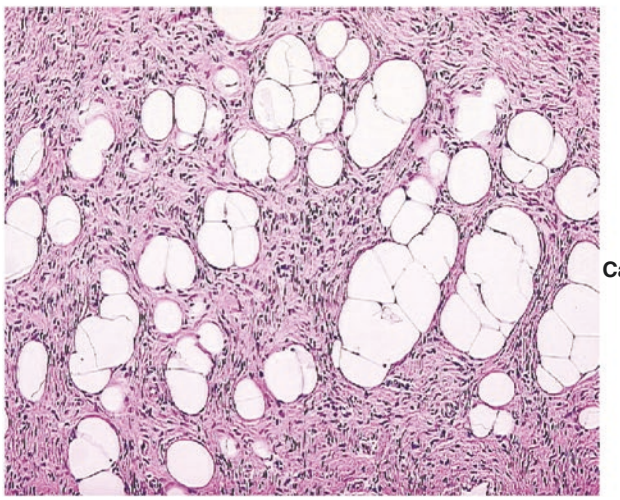


DERMATOFIBROMA *MEDIUM* 14-19



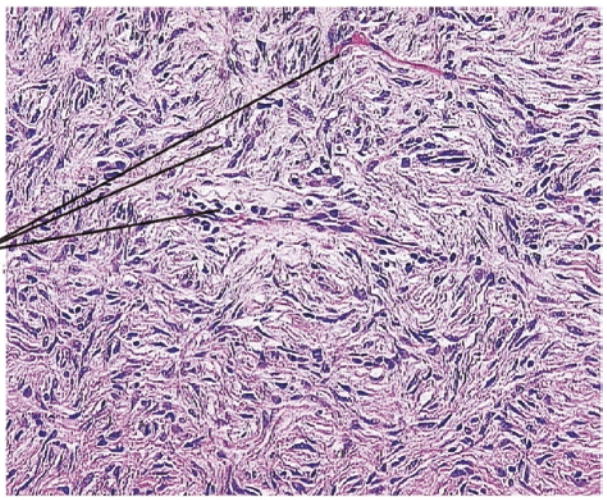
DERMATOFIBROMA *HIGH* 14-20

- Tighter bundles
- More pleomorphic spindled cells



DERMATOFIBROSARCOMA *MEDIUM* 14-21

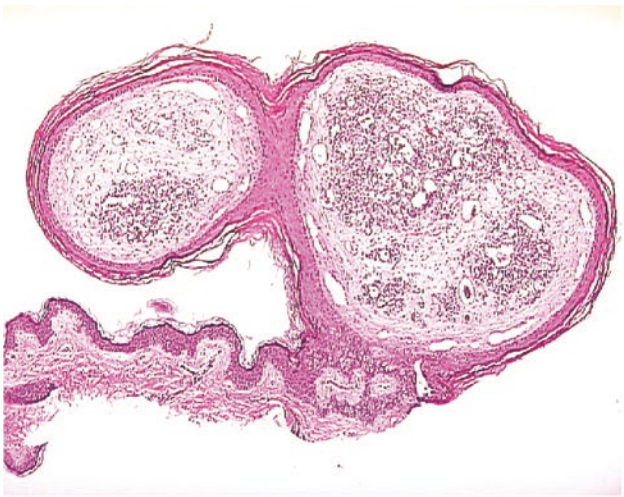
- Characteristic swiss cheese like extension of tumor into subcutaneous fat forming swiss-cheese or sieve-like orientation



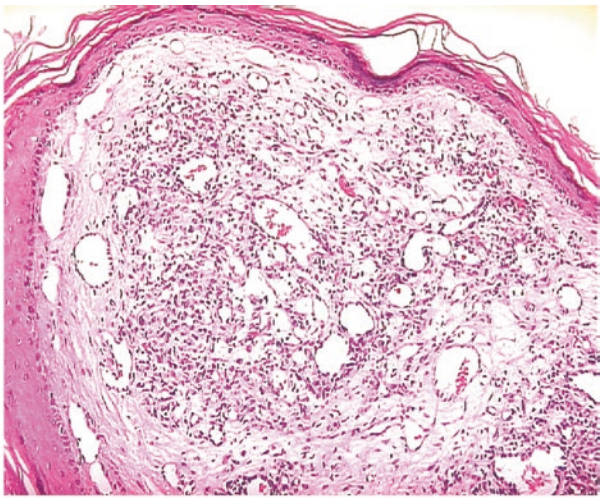
DERMATOFIBROSARCOMA *HIGH* 14-22

- Looser bundles
- Monomorphic spindled cells
- Prominent capillaries

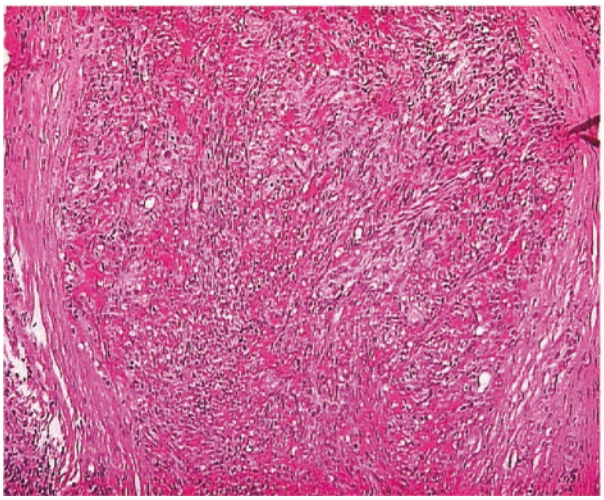
Challenges
Lobular Capillary Hemangioma / Kaposi's Sarcoma



LOBULAR CAPILLARY HEMANGIOMA 14-23

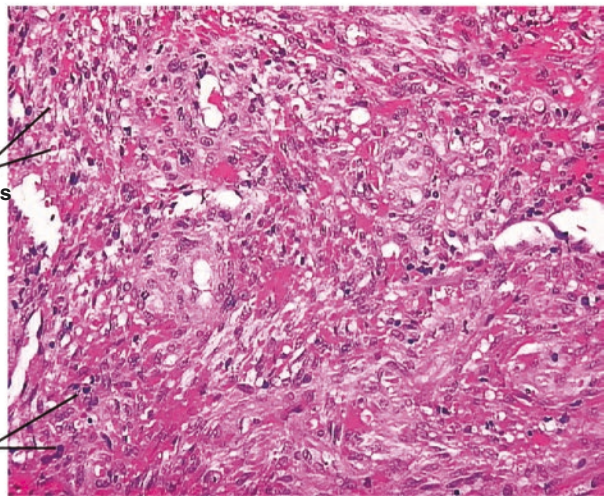


LOBULAR CAPILLARY HEMANGIOMA 14-24



KAPOSI'S SARCOMA 14-25

- Cellular neoplasm with slit-like vascular spaces

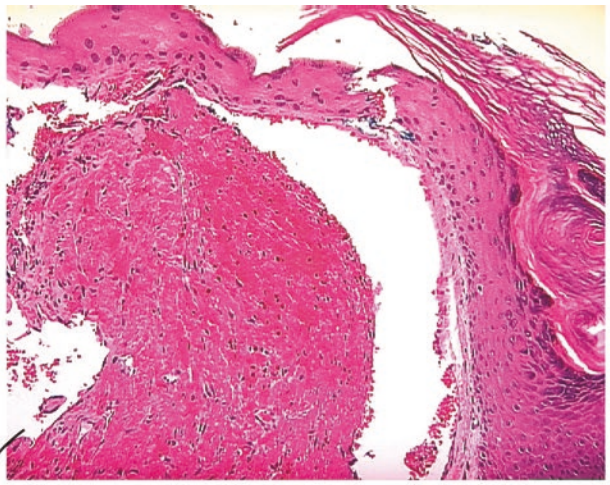


KAPOSI'S SARCOMA 14-26

- Detail of vascular neoplasm

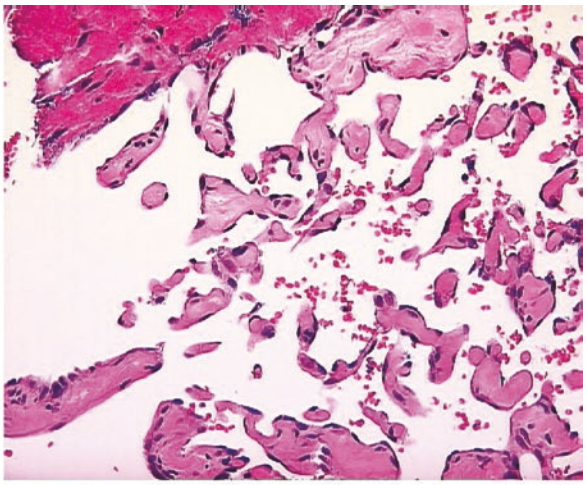
Note: Eosinophils globules
Note: Plasma cells

Challenges
Masson's Papillary Thrombosis / Angiosarcoma



THROMBOSED ANGIOKERATOMA 14-27

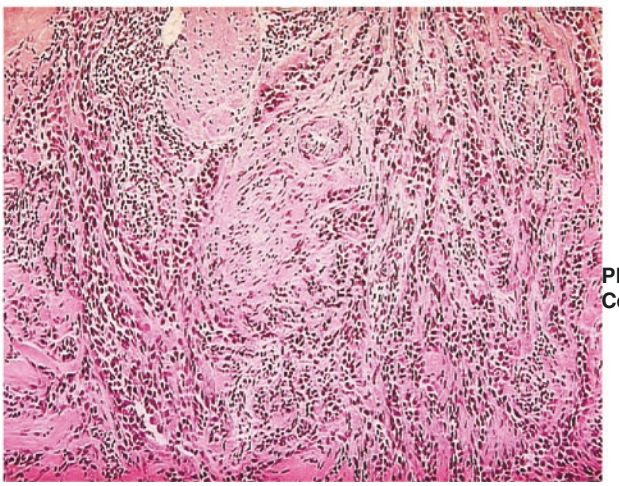
Note: Focal Masson's papillary thrombosis



MASSON'S LESION WITH ANGIOKERATOMA 14-28

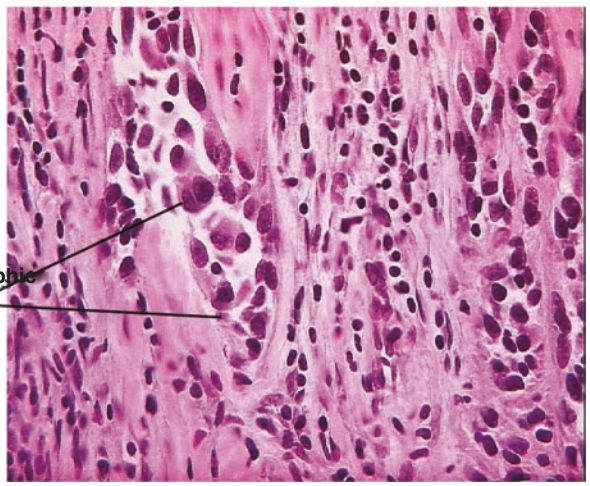
- Complex papillated growth pattern with flattened endothelia lining fibrin cores

Note: Extravasated erythrocytes



ANGIOSARCOMA *LOW* 14-29

- Deeply extending sinusoids



ANGIOSARCOMA *HIGH* 14-30

- Pleomorphic cells lining vascular spaces

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The Sarcomas

15

Aaron M. Bruce and James M. Spencer

EPIDEMIOLOGY: Collectively uncommon with exception of AFX, seen principally in elderly, equal gender.
PATHOGENESIS: AFX and AS–*UV* light, DFSP-translocation of PDGF and collagen genes t(17;22).
PATHOLOGY: AFX-storiform, anaplasia; DFSP-storiform, no anaplasia; LS-fascicles; AS-anastomosing sinusoids.
CLINICAL: AFX-face, ulcerated papule; DFSP-nodule trunk and exts.; LS-nodules; AS- face violaceous patch.

In distinction to their soft tissue counterparts, indolent biologic tendencies render the cutaneous sarcomas amenable to excisional therapy including Mohs therapy. This chapter will examine the dermal sarcomas including atypical fibroxanthoma (AFX), leiomyosarcoma (LS), dermatofibrosarcoma protuberans (DFSP) and angiosarcoma (AS).

AFX is regarded as a common, superficial and indolent form of malignant fibrous histiocytoma. Like its more aggressive deeper soft tissue counterpart it is thought to derive from a primordial fibrocyte and histiocyte-like precursor cell imbued with overlapping genotypic, phenotypic and immunohistochemical attributes of both cell types. It is most often seen in the context of sun-damaged facial skin, particularly situated on the ear, where it presents as a rapidly growing ulcerating papule. The histology comprises spindled cells arranged in a checkerboard-like or storiform manner. The individual cells show fibroblast-like spindled cells and interspersed anaplastic mono and multinucleated epithelioid histiocyte-like cells.

DFSP is an uncommon spindle cell sarcoma of unknown origin that arises within the deep dermis, later involving spread to the subcutaneous fat and capable of ulcerating the epithelium. The pathogenesis entails a characteristic translocation of genomic material involving platelet derived growth factor and a collagen gene situated on chromosomes 17 and 22, respectively, permissive to malignant transformation. The histology is distinctive consisting of a proliferation of cytologically banal spindled cells arranged like AFX in a storiform pattern. The most important feature of this neoplasm is the manner in which the cells diffusely infiltrate the subcutaneous fat, producing a sieve-like pattern. The cells possess a characteristic immunophenotype consisting of CD-34 (+), factor 13a (−) useful in separating them from dermatofibroma which is CD-34 (−), factor 13a (+).

LS is an uncommon cutaneous sarcoma derived from the smooth muscle of the dermal erector pilae or the media of vessels within the subcutaneous fat. The pathogenesis of these tumors is unknown. Clinically, they present as rapidly growing nodules located anywhere on the skin. The pathology entails spindled cells arranged as sweeping fascicles oriented at less obtuse angles than encountered in AFX with embedded anaplastic mononucleated spindled cells possessing blunt-ended nuclei likened to the appearance of cigars surrounded by perinuclear vacuoles.

AS is an extremely uncommon and aggressive sarcoma derived from the vascular endothelia. The most important pathogenic associations include ionizing and ultraviolet irradiation to the skin. The most common presentation is of a rapidly expanding erythematous or violaceous patch on the face or scalp. The pathology typically involves superficial dermal vascular spaces and deeper compressed sinusoids lined by and filled with anaplastic epithelioid cells.

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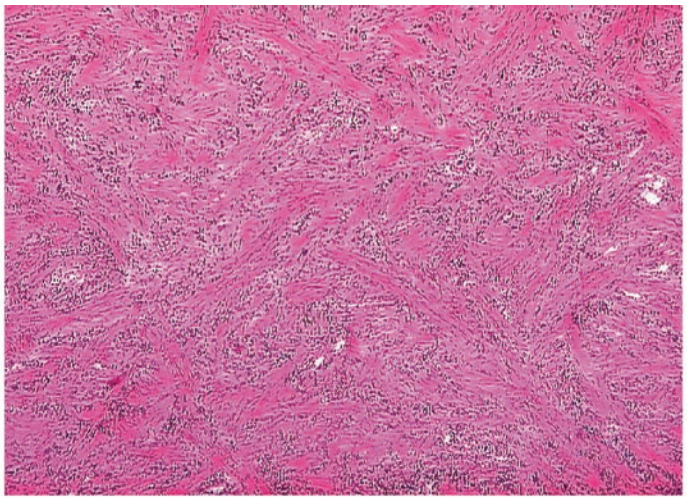
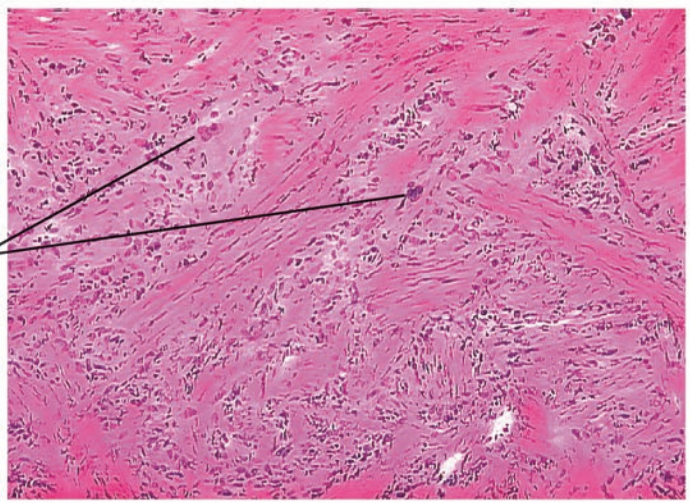
M. B. Morgan et al. (eds.), *Atlas of Mohs and Frozen Section Cutaneous Pathology*,
https://doi.org/10.1007/978-3-319-74847-4_15

Atypical Fibroxanthoma - Dermis



LOW 15-1

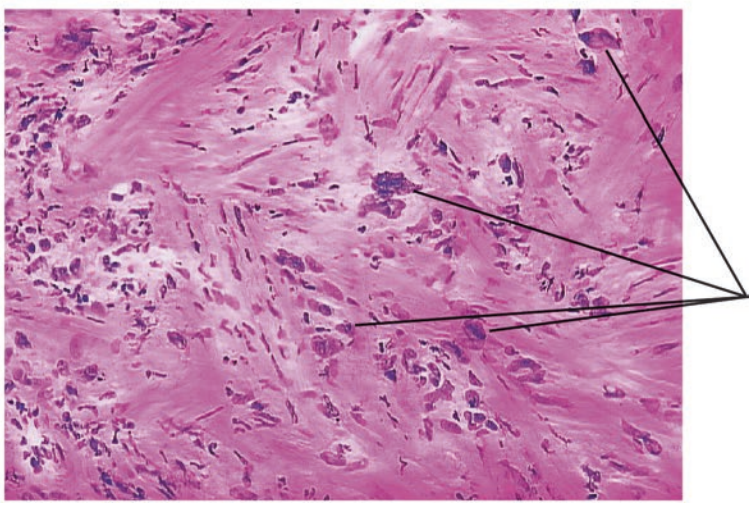
- Checker board-like pattern of tumor growth



MEDIUM 15-2

- Intersecting bundles at right angles

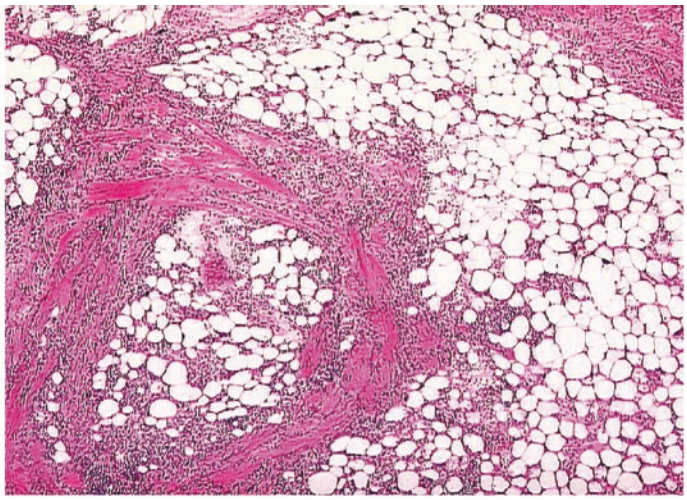
Note: Interspersed atypical cells



HIGH 15-3

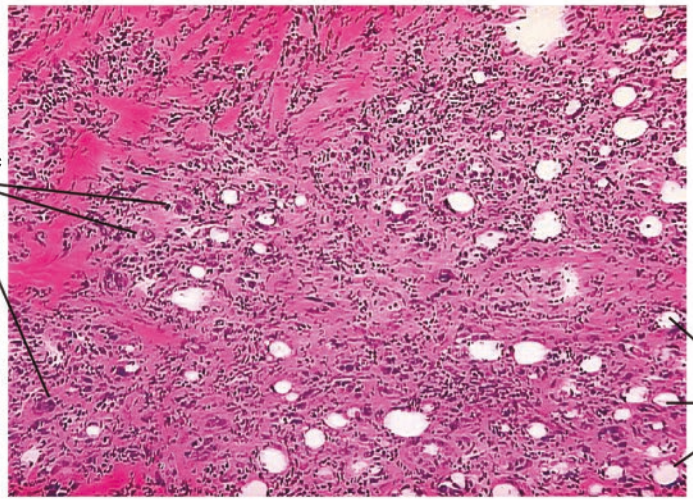
- Detail of anaplastic single and multinucleated cells

Atypical Fibroxanthoma–Subcutaneous Fat



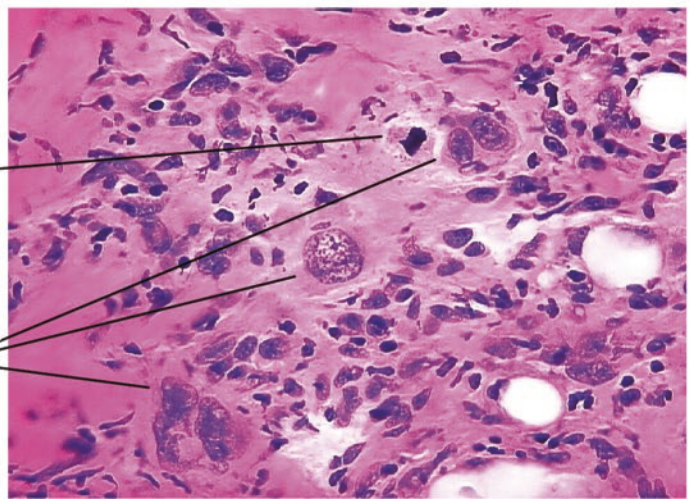
- Diffuse permeation of subcutaneous fat by atypical fibroxanthoma

LOW 15-4



- Tendency for checkerboard pattern lost in subcutaneous fat
- See remnants of fat as isolated vacuoles

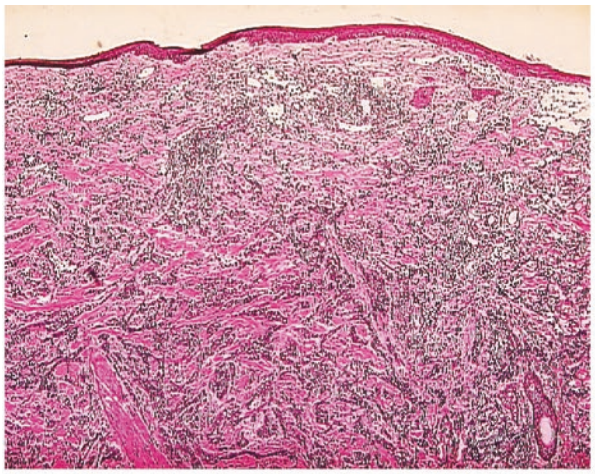
MEDIUM 15-5



- Detail of anaplastic mono and multinucleated cells

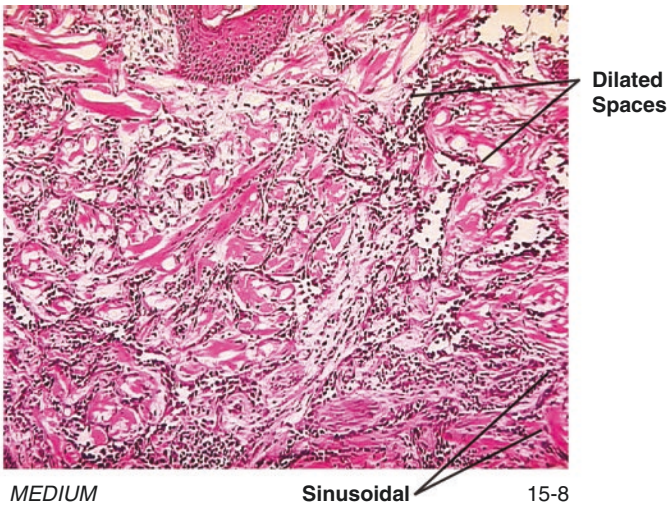
HIGH 15-6

Angiosarcoma



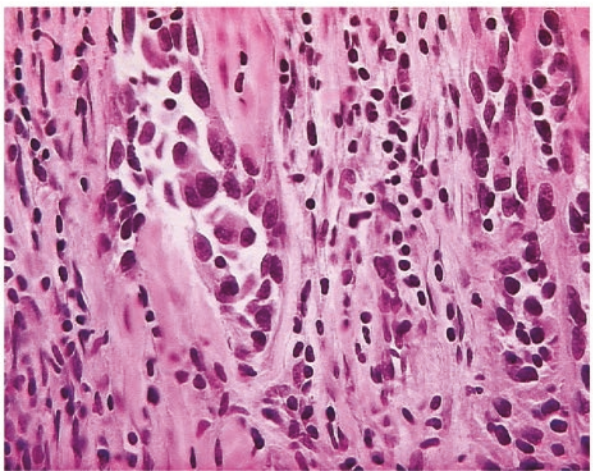
LOW 15-7

- Lower power pattern consisting of superficial dilated vascular spaces, deeper sinusoidal growth pattern



MEDIUM 15-8

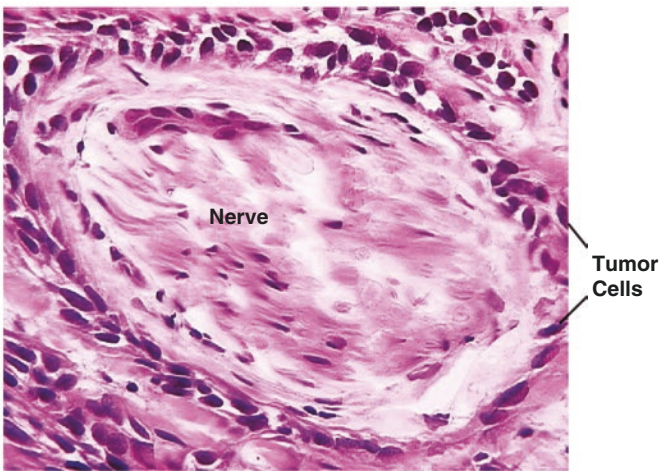
- Superficial dilated vascular spaces
- Deeper sinusoidal growth patterns



HIGH 15-9

- Detail of anaplastic tumor cells within sinusoids

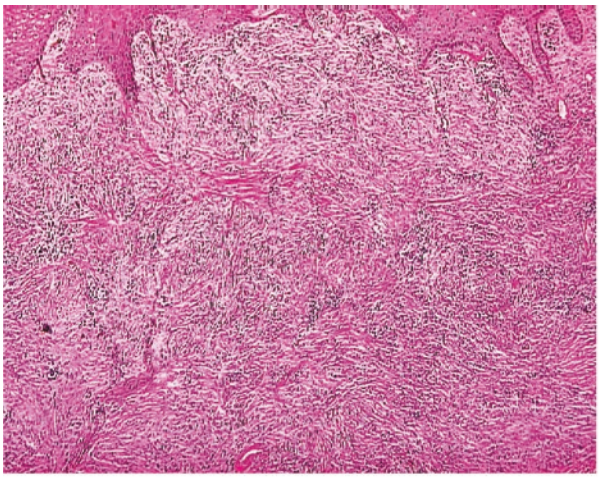
Note: Dyshesive cell pattern filling sinusoids



HIGH 15-10

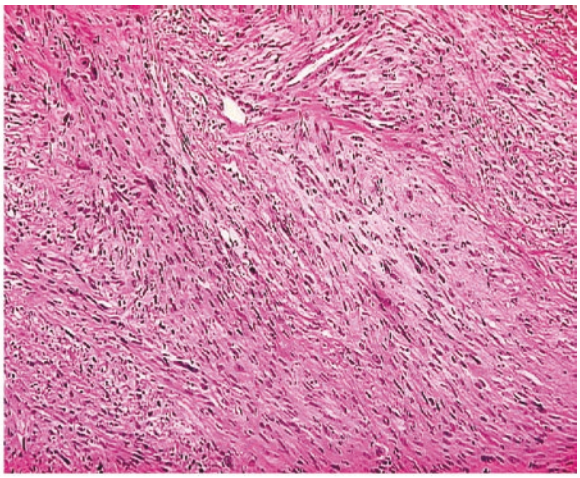
- Propensity of tumor cells to extend perineurally

Leiomyosarcoma



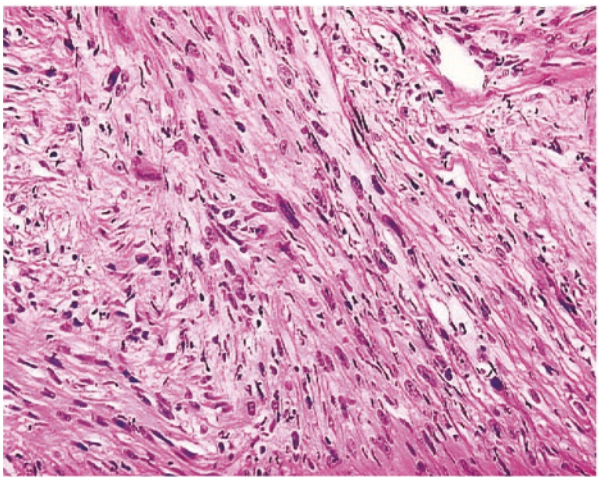
LOW 15-11

- Lower power patterns of sweeping tumor fascicles



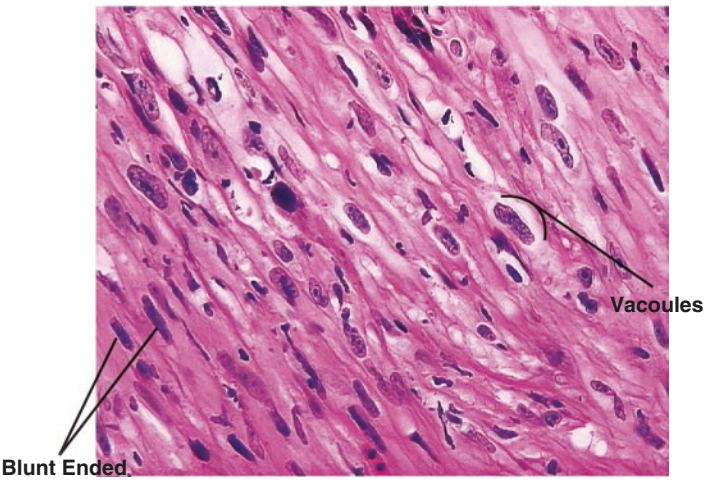
MEDIUM 15-12

Note: Tendency of spindled cells to form sweeping pattern at less obtuse angles than atypical fibroxanthoma



MEDIUM 15-13

- Detail of growth pattern



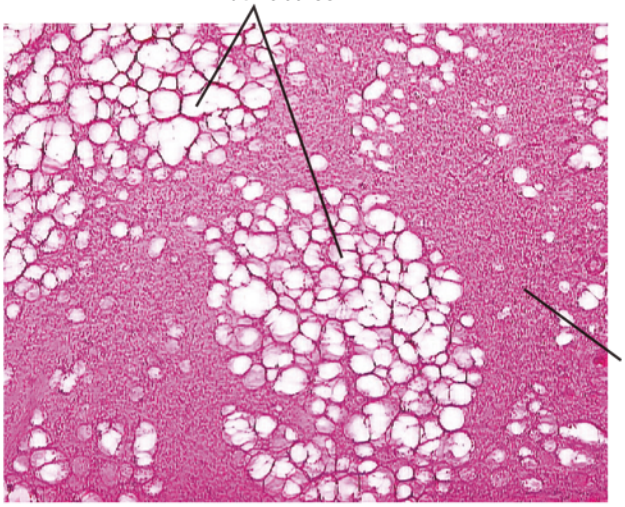
HIGH 15-14

- Detail of cells

Note: Blunt ends of nuclei likened to appearance of cigars

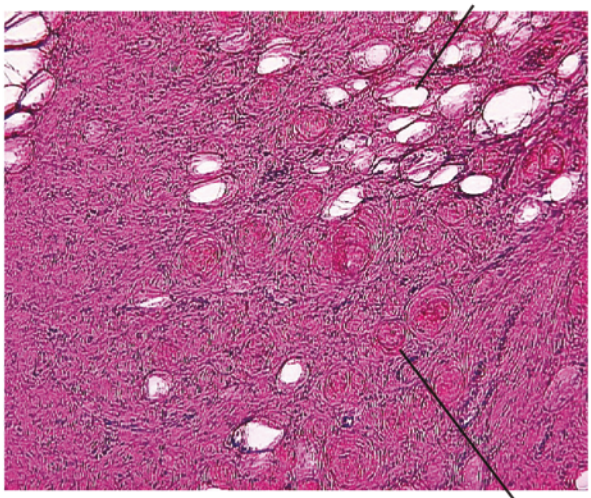
Note: Perinuclear vacuoles

Dermatofibromasarcoma Protuberans



LOW 15-15

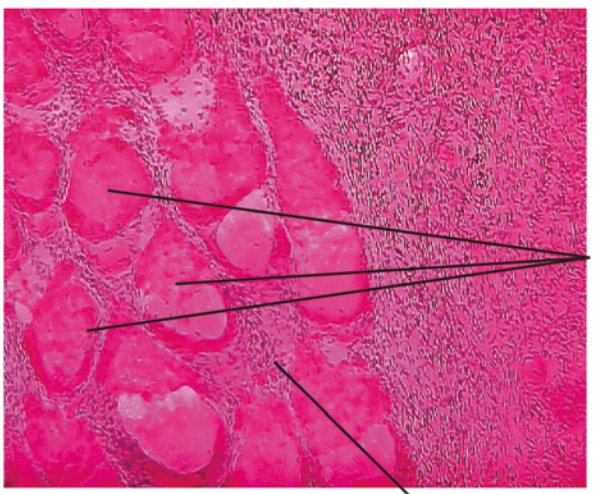
- Diffuse infiltration of the fat lobules and septae by spindle cells



MEDIUM 15-16

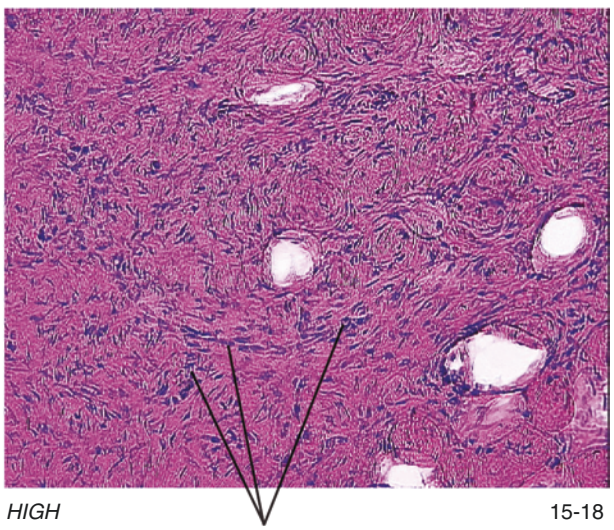
Characteristic whorling of tumor cells

- Diffuse permeation of subcutaneous fat by uniform populations of spindle cells



MEDIUM 15-17

- Spindle cells extending deep into skeletal muscle



HIGH 15-18

- Blood vessels arranged in a chicken-wire pattern

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DFSP

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Lymphoid Pathology

16

John R. Hamill Jr. and Michael B. Morgan

Lymphocytic infiltrates are near inviolate accompaniments of cutaneous dermal pathology. Lymphocytes in variant numbers can be seen in the vicinity of superficial dermal vessels and the adnexae in most biopsys specimens. Increased numbers of lymphocytes may, however, represent a pathologic condition of a diverse etiology. These entities encompass a variety of inflammatory (i.e., acne/rosacea), infections (i.e., herpes simplex virus) and neoplastic (i.e., lymphoma) conditions. Each of these diseases' states with particular attention to its histologic presentation in the setting of frozen sections or Mohs pathology are presumed herein.

Lymphoid and other inflammatory infiltrates of the skin can pose significant quandary particularly in the setting of frozen section microscopic analysis. Efforts to elucidate among benign or reactive lymphocytic and malignant dermal infiltrates can be accomplished with the aid of special techniques such as gene rearrangment studies, immunohistochemical methods or flow cytometry. However, histologic criteria remain the most important means of establishing a diagnosis readily available to the microscopist. The most important and/or common source of lymphoid infiltrates encountered at frozen section entails perineural lymphoid inflammation in the setting of perineural carcinoma extension (to be discussed in a subsequent chapter), and acneiform perifolliculitis as typically encountered in the clinical setting of adult rosacea. The latter circumstance entails a lymphocyte and neutrophilic predominant inflammatory infiltrate seen in proximity to a follicle, particularly involving the base or its mid-portions. The most important entities, though certainly less common to distinguish, are psuedolymphoma otherwise referred to as cutaneous lymphoid hyperplasia or lymphocytoma cutis and cutaneous lymphoma/leukemia. Psuedolymphoma can be encountered in any cutaneous site, and while classically seen in conjunction with persistent insect bites or vaccination, it is most often idiopathic. The typical presentation involves multiple rounded or nodular superficial dermal infiltrates. The infiltrates may contain lymphoid follicles and usually are composed of an admixture of inflammatory cell types including scattered histiocytes, eosinophils and plasma cells. One of the most important and reliable means of separating these infiltrates from lymphoma is the presence of prominent capillaries containing enlarged endothelia. Cutaneous lymphoma is an uncommon occurrence that classically presents in the guise of a solitary violaceous nodule on the face or scalp and in the absence of systemic signs. The infiltrates tend to involve the superficial and deeper dermis and subcutaneous fat and are composed of a paradoxically uniform population of small lymphocytes. The other manner in which lymphoma may present is as a secondary or metastatic lesion in a patient with established or bone marrow/lymph node disease. These infiltrates tend to be quite dense, deep seated and comprising larger or anaplastic-appearing lymphocytes. Leukemic infiltrates may present *de novo* as dense collections of abnormal hematopoetic cells possessing angulated nuclear contours. Among the more helpful ways of estab-

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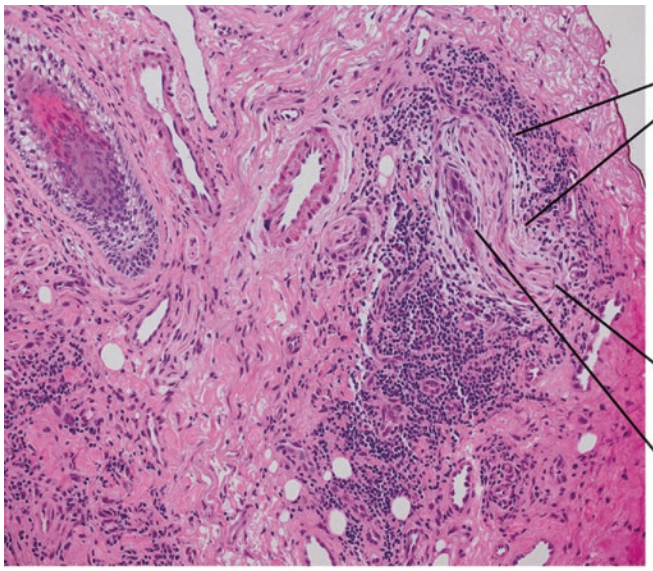
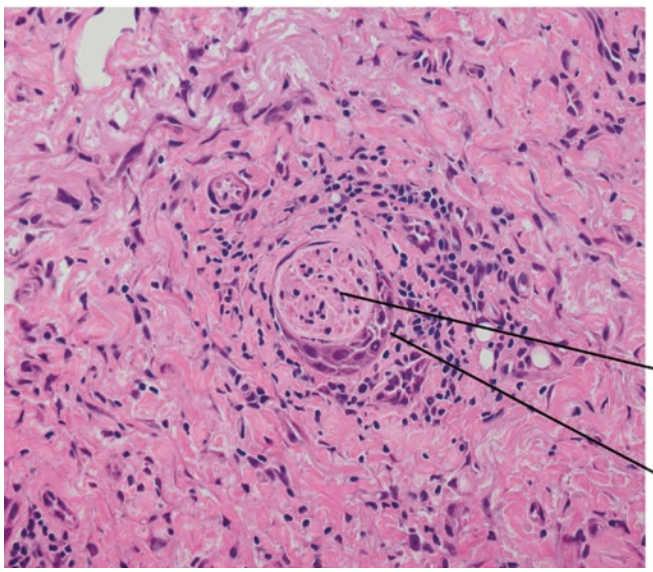
lishing a presumptive diagnosis is looking for the presence of a pathology-free superficial dermal corridor known as the Grenz zone seen in the majority of these cases. Lymph nodes can be rarely seen in the deeper dermis or subcutaneous fat. They typically are well-circumscribed by a capsule and possess internodal zonation due to the presence of rounded follicles with germinal centers and interfollicular areas. A characteristic feature of lymph nodes entails the presence of a capsule and a subcapsular pale zone or marginal sinus.

Perineural InvasionLymphoid Aggregates

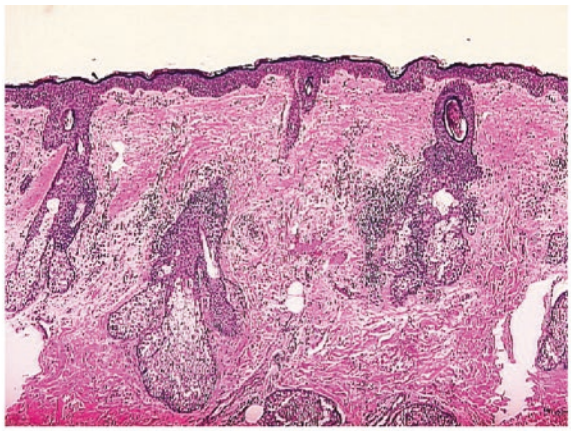


LOW 16-1



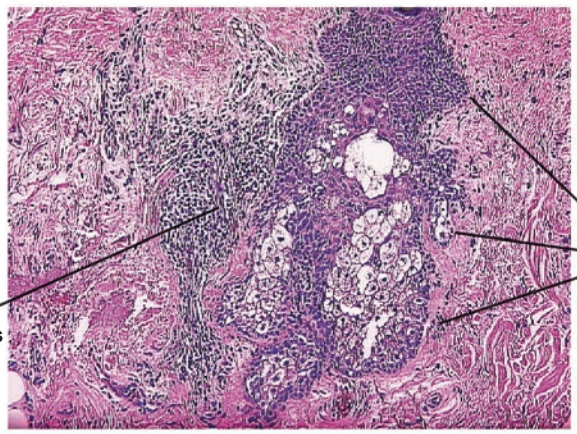
MEDIUM 16-2

Rosacea



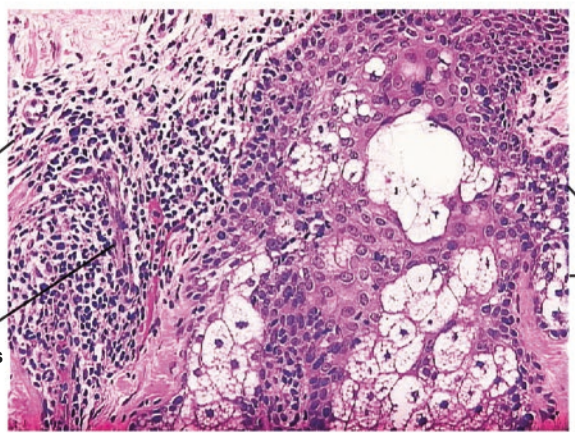
- Perifollicular nodular lymphoid infiltrates

LOW 16-3



Note: Juxtaposition of lymphocytes to follicle

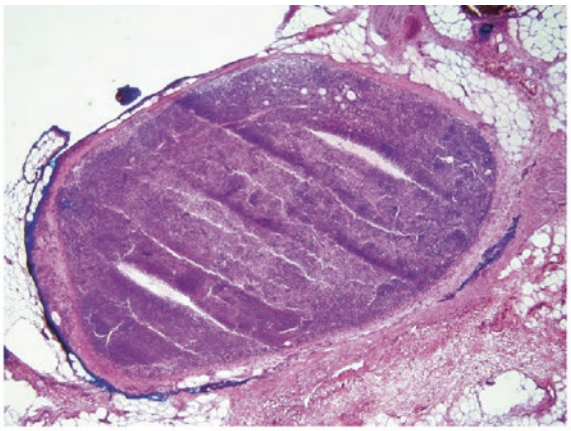
MEDIUM 16-4



- Details of lymphocytes around blood vessels (telangectases) and follicle

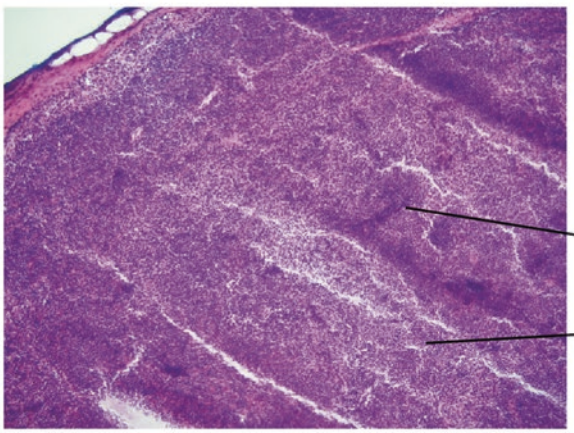
HIGH 16-5

Lymph Node



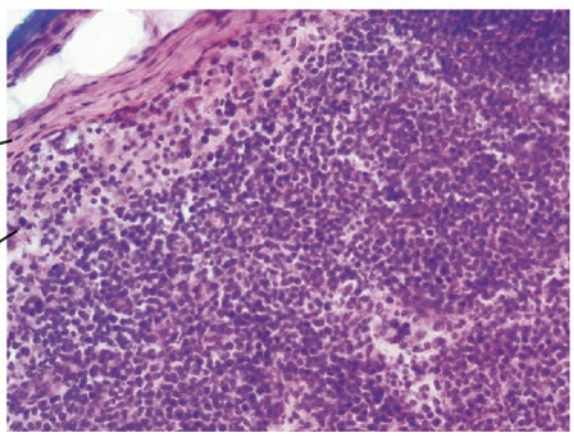
LOW 16-6

- Well circumscribed deep dermal/ subcutaneous fat nodule



MEDIUM 16-7

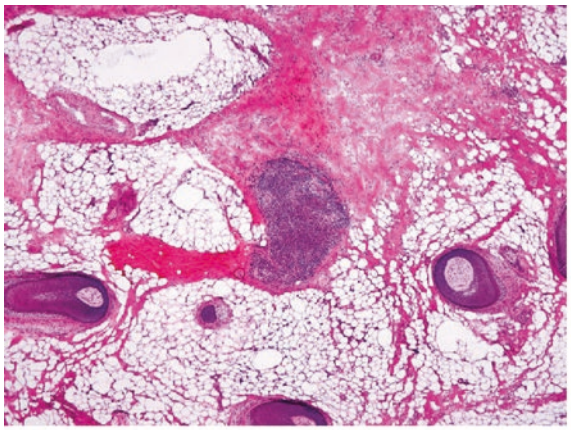
- Typical zonation of reactive lymph node with follicular and perifollicular areas



HIGH 16-8

- Detail of lymph node capsule and marginal sinus

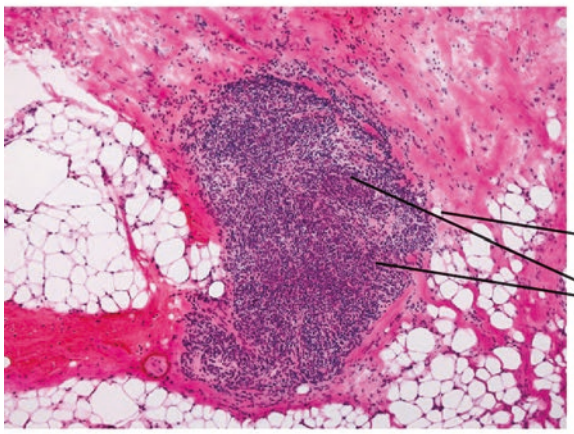
Nodular Lymphoid Infiltrate-SCC



LOW 16-9

- Nodular lymphoid infiltrate

Note: Lack of association with blood vessels or adnexae

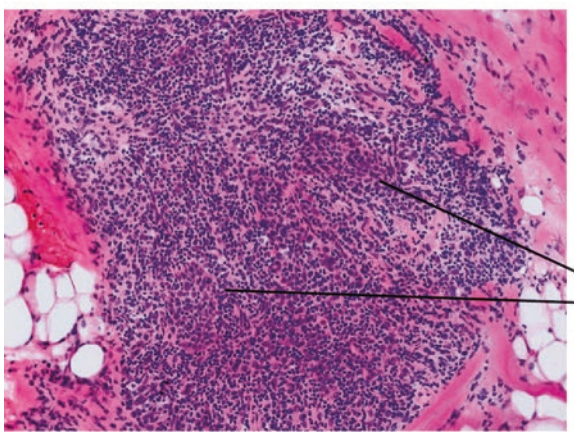


MEDIUM 16-10

- Detail of lymphoid infiltrate with two-toning

Dark Purple Zone (Lymphocytes)

Light Red Zone (SCC)

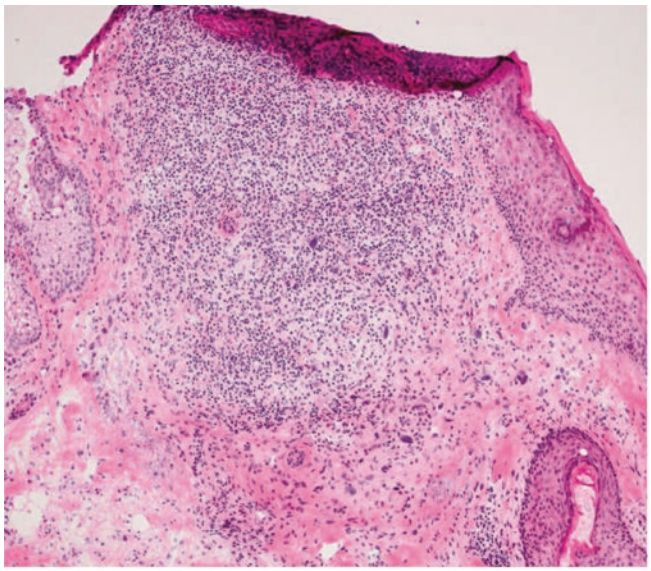


HIGH 16-11

- Detail of lighter red staining squamous cells (SCC) obscured by lymphocytes

SCC

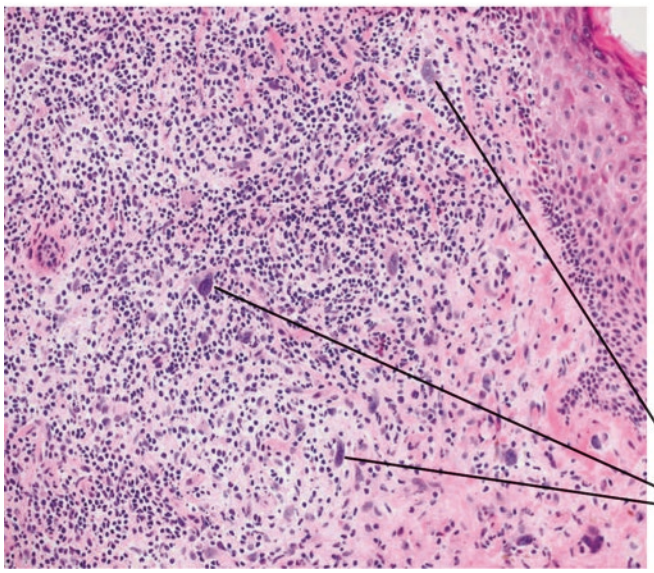
Nodular Lymphoid Infiltrate-SCC



LOW 16-12

- Nodular lymphoid infiltrate

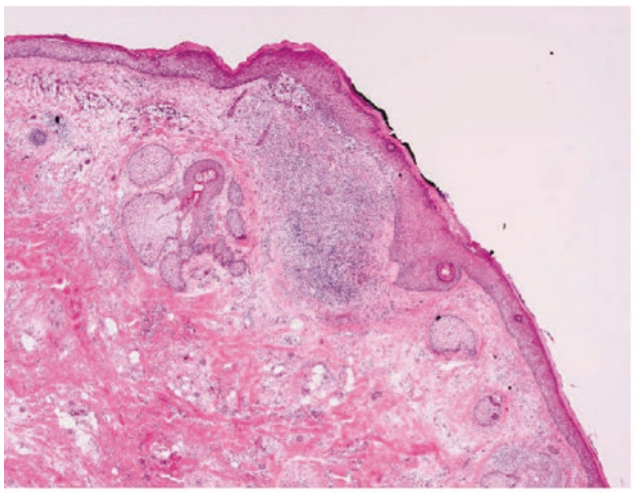
Note: Lack of association with follicle or blood vessels



HIGH 16-13

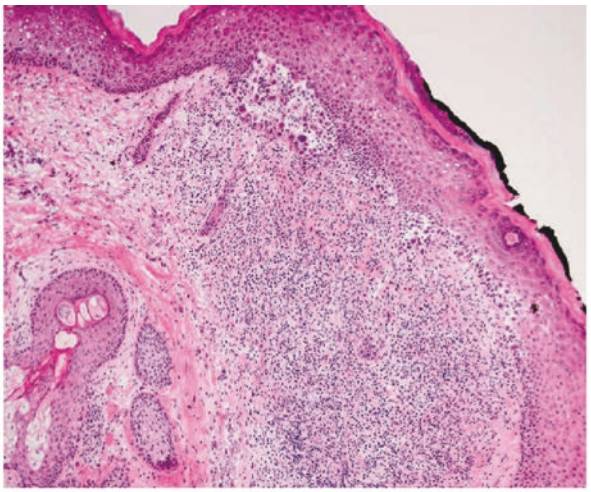
- Detail of interspersed poorly differentiated SCC cells

Nodular Lymphoid Infiltrate-SCC



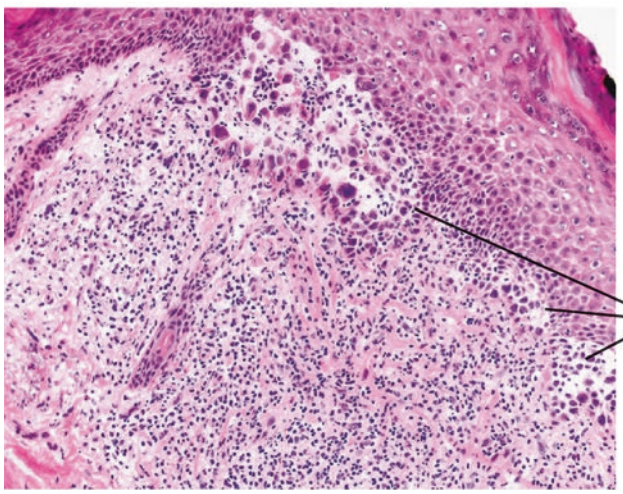
LOW 16-14

- Nodular lymphoid infiltrate in close proximity to epithelium



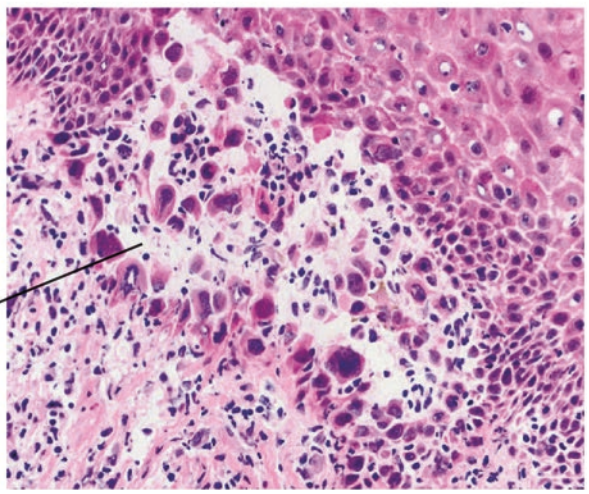
MEDIUM 16-15

- Detail of inflammation obscuring SCC



HIGH 16-16

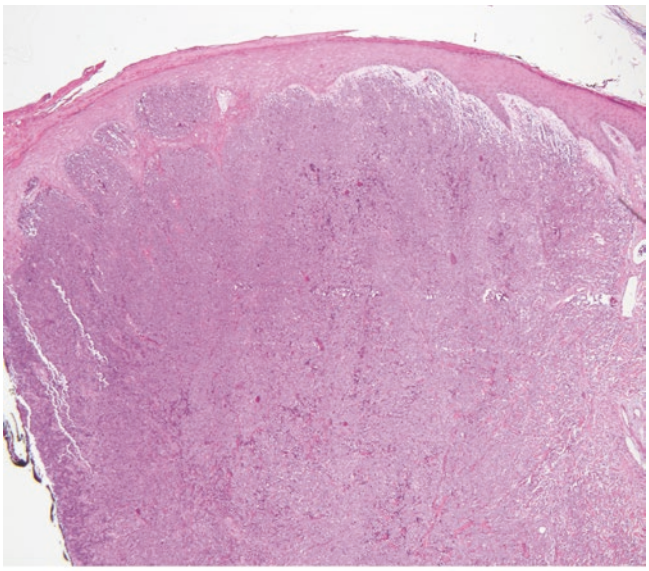
- Acantholytic SCC



HIGH 16-17

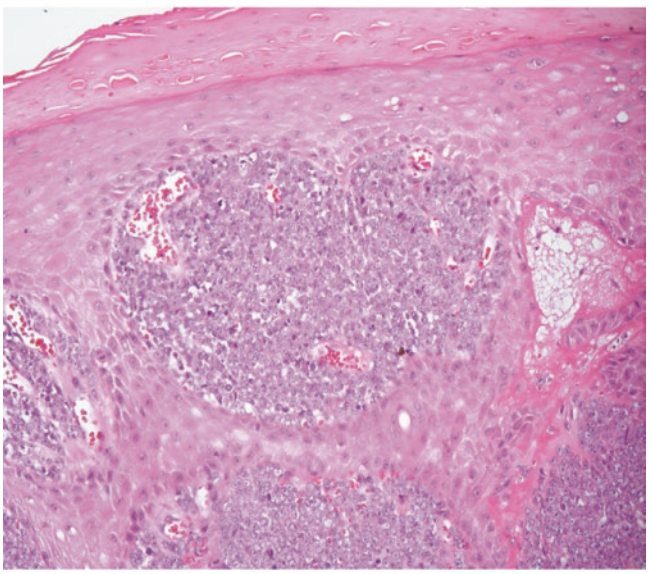
- Free floating dyskeratotic epithelial cells of SCC

Systemic B-Cell Lymphoma



LOW 16-18

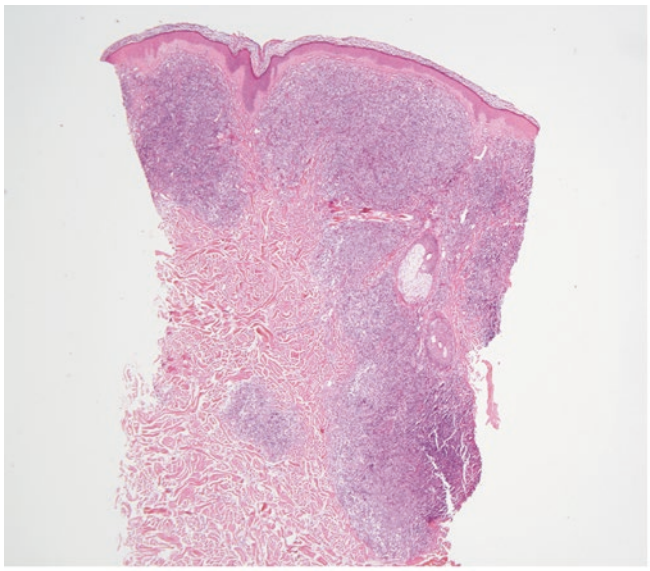
- Diffuse dermal infiltrate



MEDIUM 16-19

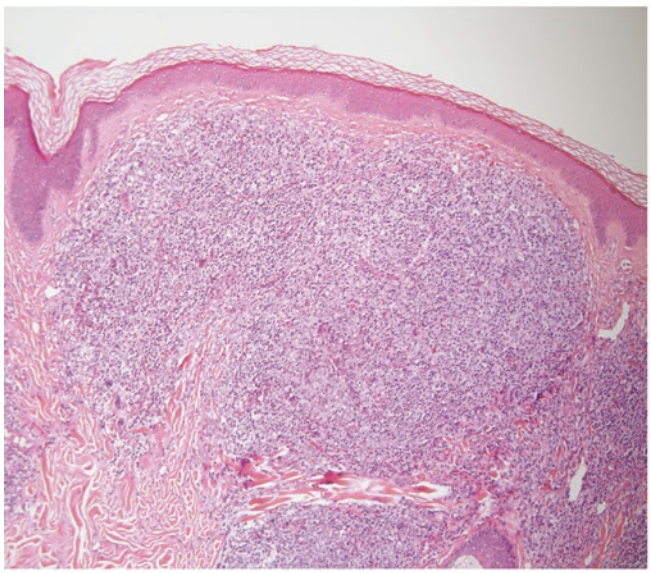
- Uniform population of densely compressed atypical lymphocytes

Low Grade Cutaneous B-Cell Lymphoma



LOW 16-20

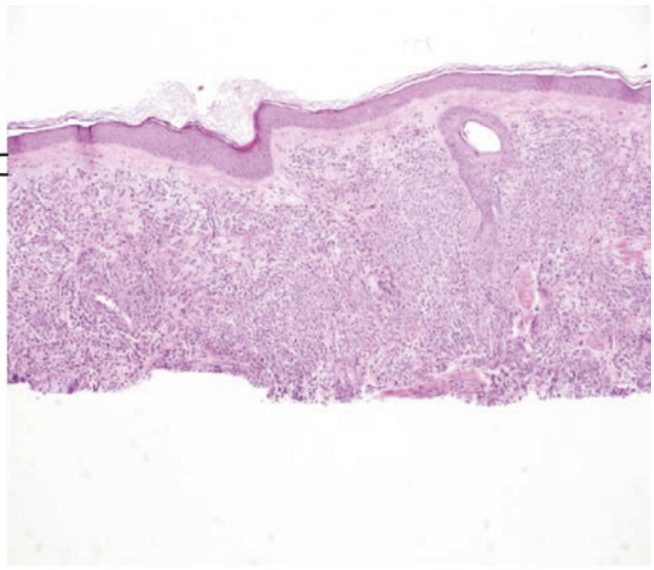
- Superficial and deep dermal infiltrate



MEDIUM 16-21

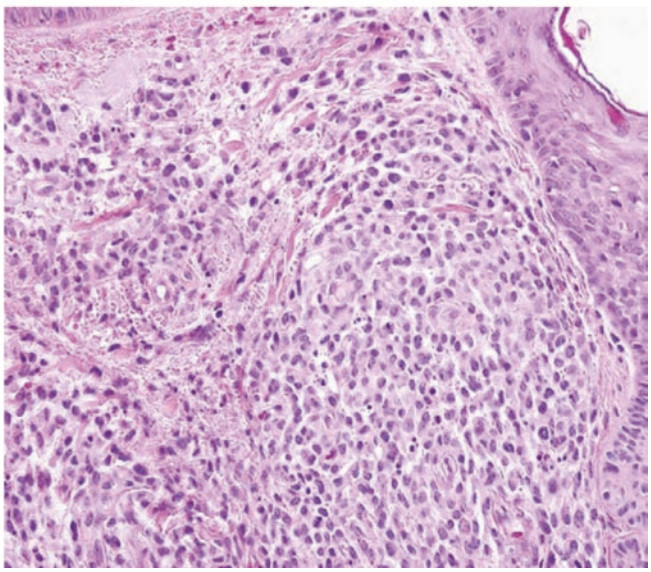
- Uniform population of atypical lymphocytes

Leukemia Cutis



LOW 16-22

- Dense dermal infiltrate
- Grenz zone



MEDIUM 16-23

- Uniform population of angulated primordial hematopoetic cells

Bibliography

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3. Su W, Buechner S, Li C. Clinicopathologic correlations in leukemia cutis. J Am Acad Dermatol. 1984;11:121.

Part IV

Special Topics

Perineural Pathology

17

Martin Dunn

EPIDEMIOLOGY: Up to 6% of squamous cell carcinomas (SCC) and 3% of basal cell carcinomas (BCC).
ETIOLOGY: As with BCC and SCC, primarily accumulated ultraviolet exposure.
PATHOGENESIS: Upregulation of TGF-beta, with resulting downregulation of epithelial-cadherin and overexpression of (neural)-cadherin. Other cell adhesion molecules including caveolin-1 (cav-1) and bystin may be involved.
CLINICAL: Associated with other signs of aggressive cancers such as large size (>2 cm), Breslow level (>4 mm) and more aggressive histologic subtypes. Most common anatomic locations include the lip, ear, forehead, scalp, temple and dorsal hand. Cancers with PNI are more likely to present to the Mohs surgeon as recurrences either from traditional surgical excision or from previous Mohs surgeries. Neurologic signs or symptoms may be present.
HISTOLOGY: In the immediate presence of a non-neural dermal malignancy, PNI may be diagnosed by the observation of malignant cells in the perineural space of peripheral nerves.

Perineural invasion (PNI) is an ominous complication of any of the primary cutaneous malignancies. The presence of PNI has been associated with high recurrence rates, aggressive behavior and poor survival. The most common adverse outcome associated with PNI and skin cancer is recurrence. Leibovitch et.al. reported the results of the ten-year Australian Mohs database. Skin cancers with PNI were more likely to have been recurrent *before* coming to Mohs surgery, required more stages to clear and left a larger defect than those cancers without PNI. They were also more likely to recur *after* Mohs surgery. One of the most devastating outcomes of a cancer with PNI is leptomeningeal carcinomatosis (LMC) and death. The perineurium is an extension of the pia-arachnoid, and the perineural space is an extension of the leptomeninges. A cancer that gains the ability to invade the perineurium finds a path of low resistance in the perineural space, relatively protected from host defenses. The cancer is then able to spread in continuity from the bulk of the tumor along the perineural space of the peripheral nerve, eventually reaching the central nervous system. The great majority of patients with LMC have no evidence of lymph node metastases, confirming that the process of PNI is distinct from the process of metastasis. Most case reports of patients with a head and neck primary cancer that spreads via PNI into the cranial nerves and CNS suggest that this is a slow process. In some cases, patients reported many years of neurological symptoms prior to diagnosis. It is suggested that the earlier the diagnosis of PNI is made, the better the prognosis. Patients with a cutaneous SCC with "incidental asymptomatic" PNI have at least an 80% cure rate, compared to 45% cure rate for those with clinically evident PI. When the PNI extends to the skull base, the local control rate is only 25%. The Mohs surgeon typically deals with primary cutaneous malignancies at a much earlier stage of development than similar cancers of the aerodigestive tract or the deeper tissues of the head and neck. The process of PNI tends to develop early in the course of skin cancers, extends contiguously from the primary site of the cancer, and pursues an indolent natural course. All are qualities that make PNI amenable to extirpation via the Mohs technique. A stratification of PNI into "microscopic" versus "extensive" has been proposed, for the purpose of improving future outcome studies.

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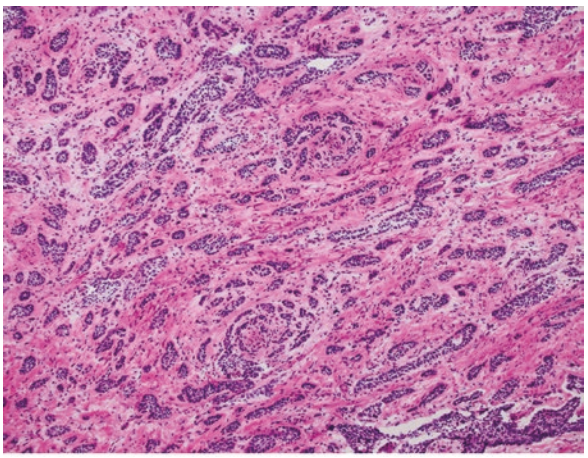
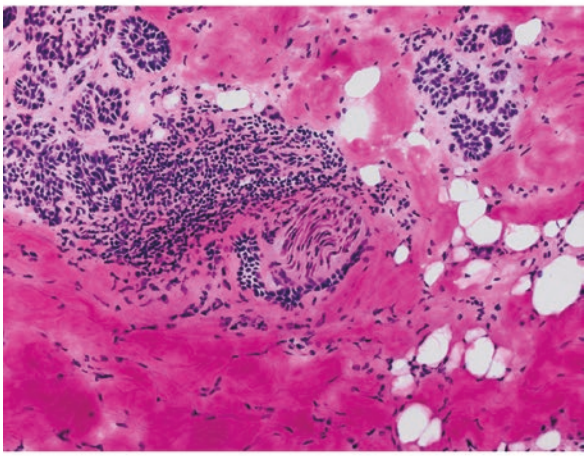
https://doi.org/10.1007/978-3-319-74847-4_17

Perineural Invasion
Basal Cell Carcinoma



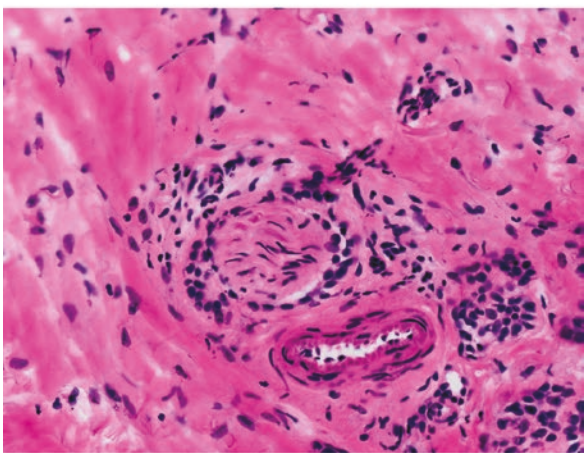
BASAL CELL CARCINOMA *LOW* 17-1

- Aggressive histologic subtype (infiltrating)



BASAL CELL CARCINOMA *MEDIUM* 17-2

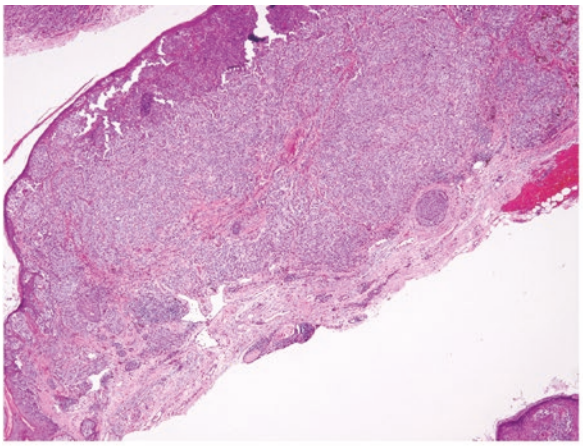
- Dense inflammation
- Obvious association with the body of the tumor



BASAL CELL CARCINOMA *HIGH* 17-3

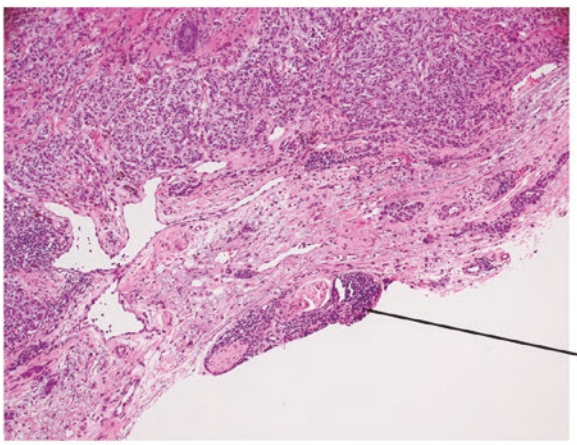
- Malignant cells in the perineural space

Perineural Invasion
Malignant Melanoma



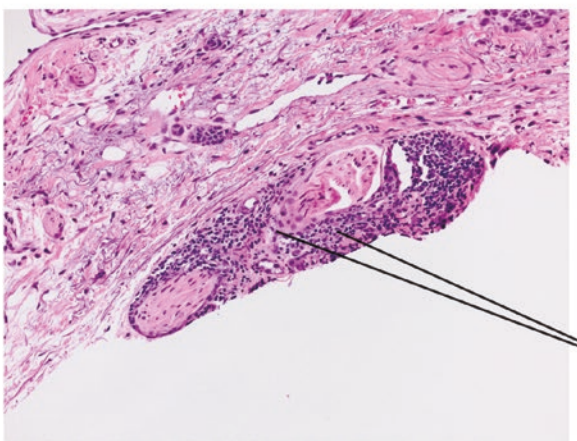
MALIGNANT MELANOMA *LOW* 17-4

- Obvious association with the body of the tumor
- Dense inflammation in the area



MALIGNANT MELANOMA *MEDIUM* 17-5

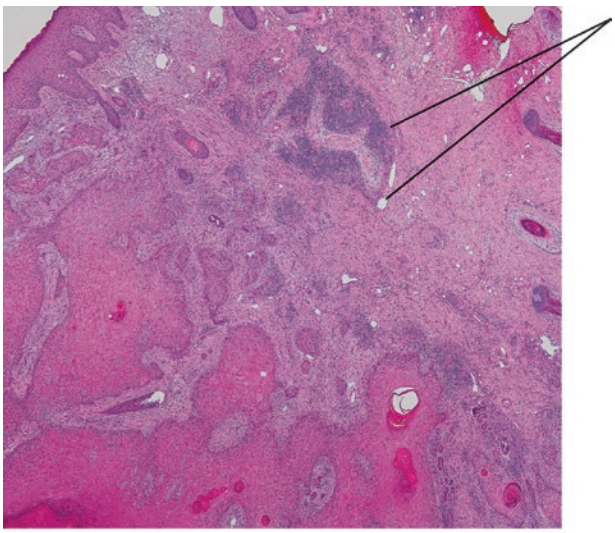
- Dense perineural inflammation



MALIGNANT MELANOMA *HIGH* 17-6

- Malignant melanoma cells in the perineural space

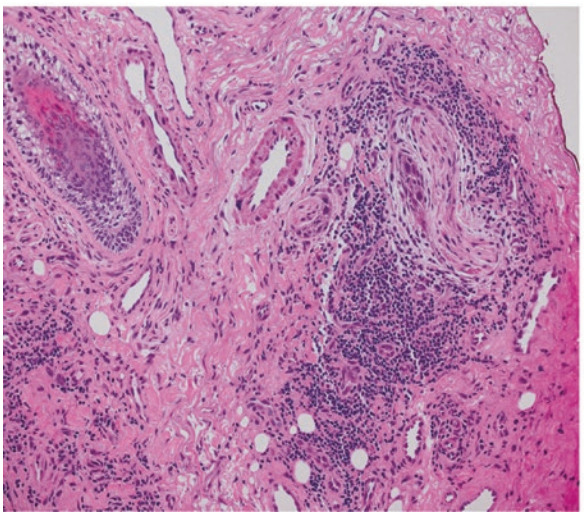
Perineural Invasion
Squamous Cell Carcinoma



SQUAMOUS CELL CARCINOMA *LOW* 17-7

- Dense inflammation in the area immediately surrounding peripheral nerves
- Obvious association with the body of the tumor

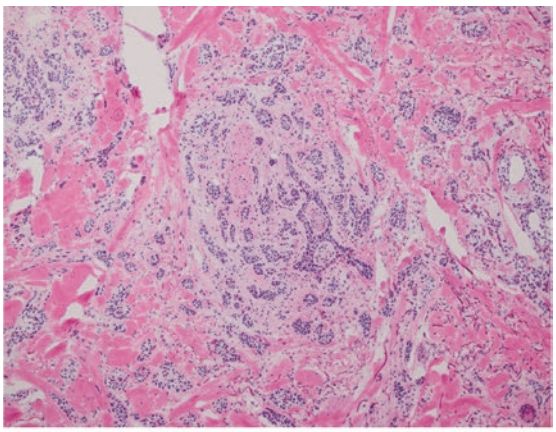
Note: Cuff of lymphocytes surrounding nerve



SQUAMOUS CELL CARCINOMA *MEDIUM* 17-8

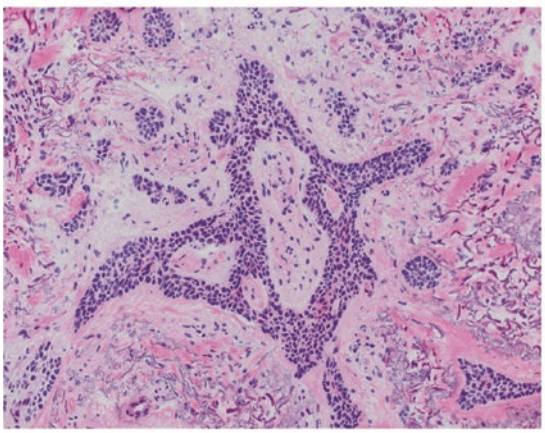
- Tangential and cross sections of involved nerves
- Dense perineural inflammation

Perineural Invasion Challenges
Peritumoral Fibrosis (PF)



PERITUMORAL FIBROSIS *MEDIUM* 17-19

- Peritumoral fibrosis refers to the presence of concentric rings of fibrous tissue that together with nests of tumor cells may mimic PNI

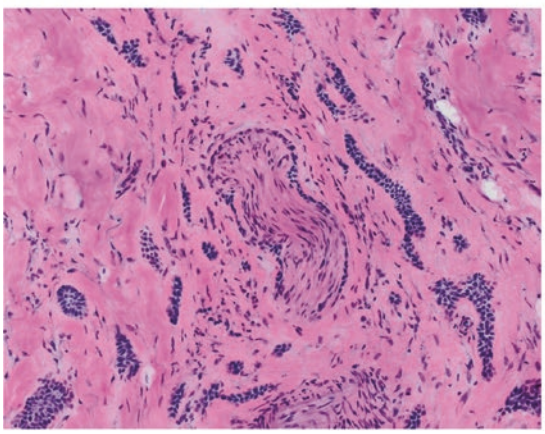


PERITUMORAL FIBROSIS *HIGH* 17-20

- Fibrous tissue surrounded by infiltrating BCC resembles nerve tissue

Note: The absence of the characteristic foamy, wavy cytoplasm of nerve tissue

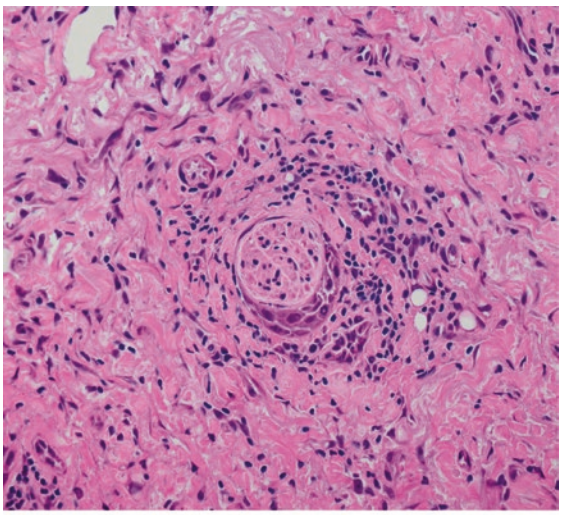
Note: The nuclei are not elongated and wavy as they are in nerve tissue



PNI *HIGH* 17-21

- Involved nerve is identified by the elongated wavy nuclei as well as the characteristic foamy cytoplasm of nerve

Perineural Invasion Challenges
RPI/RNEA

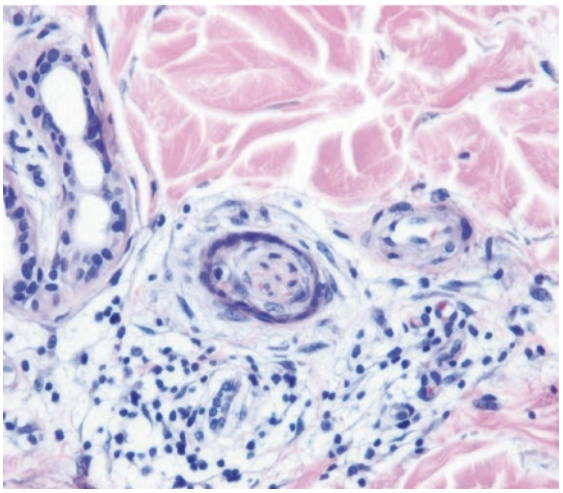


RPI *HIGH* 17-12

Note: Perineural scarring as seen in a re-excision specimen

- Re-excision perineural invasion **(RPI)** and reactive neuroepithelial aggregates of the skin **(RNEA)** refer to the presence of mature squamous cells in the perineural space of peripheral nerves

- **RPI/RNEA** is seen in re-excision specimens, as well as inflammatory



RPI/RNEA *HIGH* 17-13

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Cytopathology of Cutaneous Tumors

18

Kenneth B. Calder, Rahel Mathew, and Michael B. Morgan

Cytopathology is the study of morphologic cellular features based upon microscopic anatomy. In addition, the cytologic findings of cells reflect functional differentiation (cytoplasm) and cellular activity (nuclear findings). Understanding the cellular details of neoplasms has significant diagnostic utility. The cytologic features of the most common skin tumors are presented in this chapter.

Squamous Cell Carcinoma

The features most characteristic of squamous cell carcinoma (SCC) include a substantial increase in the nuclear cytoplasm ratio, an eosinophilic cytoplasm and the presence of intercellular bridges. Other features that assist in the diagnosis of SCC include pleomorphic cells, which may have a mosaic tile arrangement, and the presence of hyperchromatic nuclei with an irregular chromatin pattern.

Basal Cell Carcinoma

The malignant cells of a basal cell carcinoma (BCC) are cohesive, monotonous and overcrowded. The cells have very high nuclear to cytoplasmic ratios. The cells are small to intermediate with oval, elongated and hyperchromatic nuclei with occasional inconspicuous nucleoli. Peripheral palisading of the nuclei can be seen.

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Basosquamous Carcinoma

Basosquamous carcinoma is a distinct entity with overlapping cytohistologic features of both BCC and SCC. The cells of basosquamous carcinoma are spindle shaped with an eosinophilic cytoplasm (keratinization), similar to SCC. On the other hand, there are also cytologic features of BCC as well: peripheral palisading and stromal fibroplasia.

Melanoma

The epithelioid cells of melanoma tend to be medium to large sized, round to polyhedral, with prominent cellular polymorphism. An abundant granular cytoplasm with intracytoplasmic melanin granules is also present. Nuclear features include: relatively large nuclei, with or without intranuclear inclusions, and prominent "cherry red" macronucleoli. Nuclear pleomorphism, a high mitotic rate with atypical mitoses, as well as bi- or multinucleation is also usually present.

Merkel Cell Carcinoma

The cells of merkel cell carcinoma are monomorphic, loosely cohesive with nuclear molding. Tumor cells are intermediate in size, round to oval with fine granular and diffuse chromatin pattern and inconspicuous nucleoli. There is only a thin rim of cytoplasm, thereby increasing the nuclear to cytoplasmic ratio.

M. B. Morgan et al. (eds.), *Atlas of Mohs and Frozen Section Cutaneous Pathology*,
https://doi.org/10.1007/978-3-319-74847-4_18

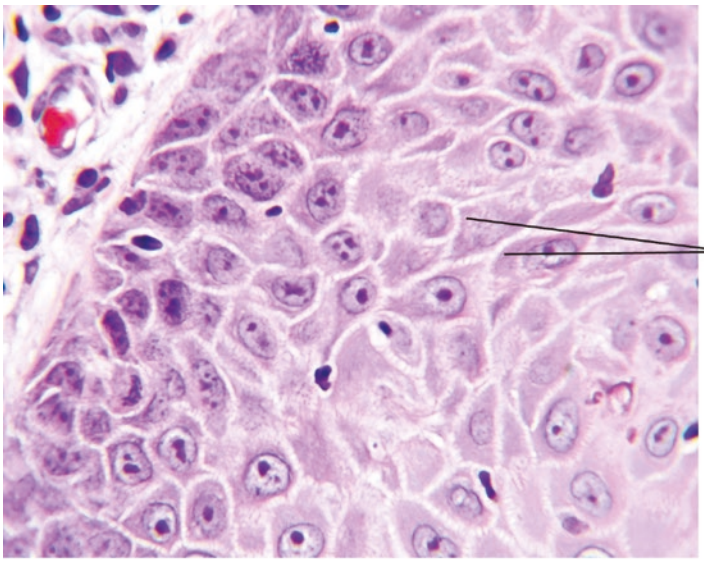
Paget's Disease

Paget's disease of the skin consists of glandular epithelium with large pleomorphic nuclei, prominent nucleoli and high nuclear to cytoplasmic ratio. The chromatin pattern is pale, and the cells can be seen singly or in small clusters.

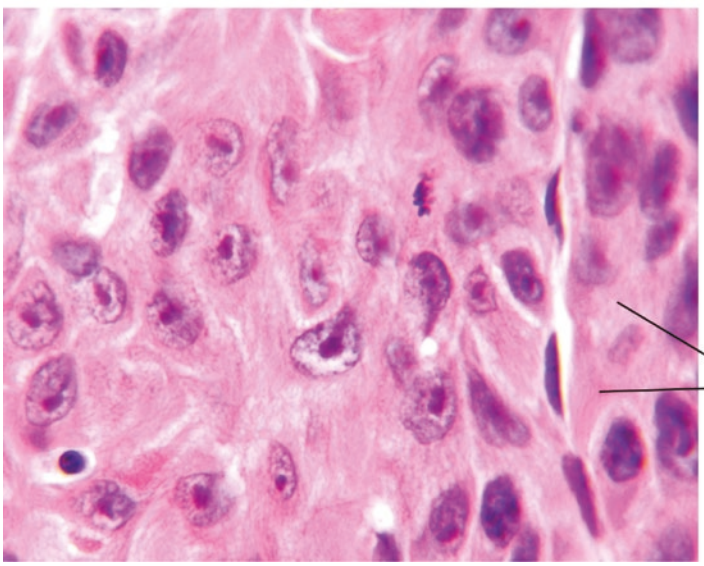
Sebaceous Carcinoma

The cytohistologic features of sebaceous carcinomas (SC) demonstrate recognizable sebaceous differentiation. Comprising confluent aggregates (lobules) of neoplastic cells of varying shapes and sizes, SC have a large bubbly cytoplasm. Malignant cytologic features include: nuclear pleomorphism, nuclear hyperchromatism and frequent atypical mitoses. The following features support sebaceous differentiation and assist in the diagnosis: large vesicular nuclei with prominent nucleoli, a foamy vacuolated cytoplasm and the presence of lipid-laden histiocytes in the background.

Squamous Cell Carcinoma

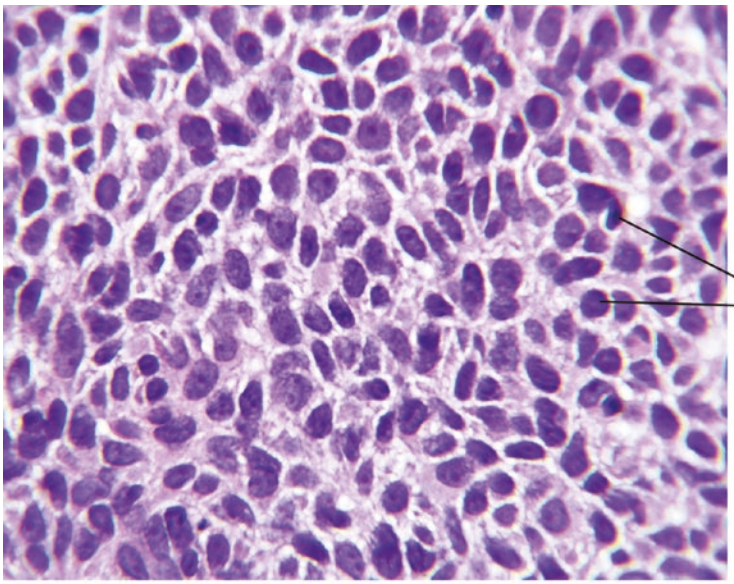


18-1



18-2

Basal Cell Carcinoma



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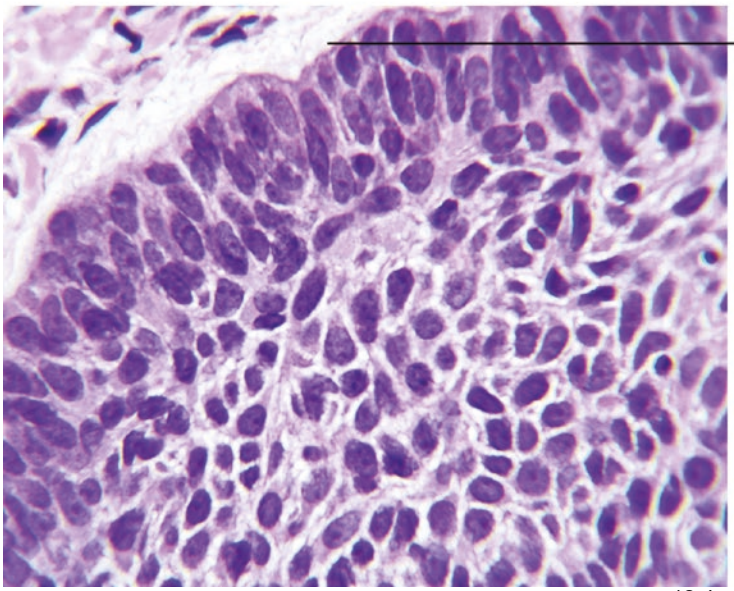
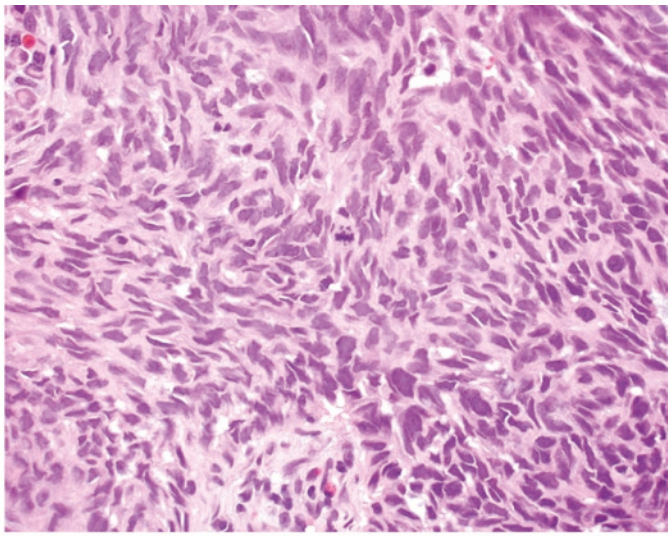


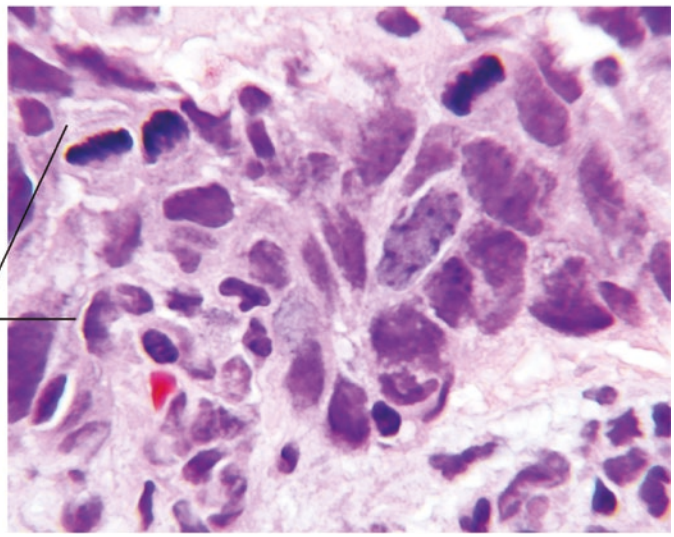
18-4

Basosquamous Carcinoma



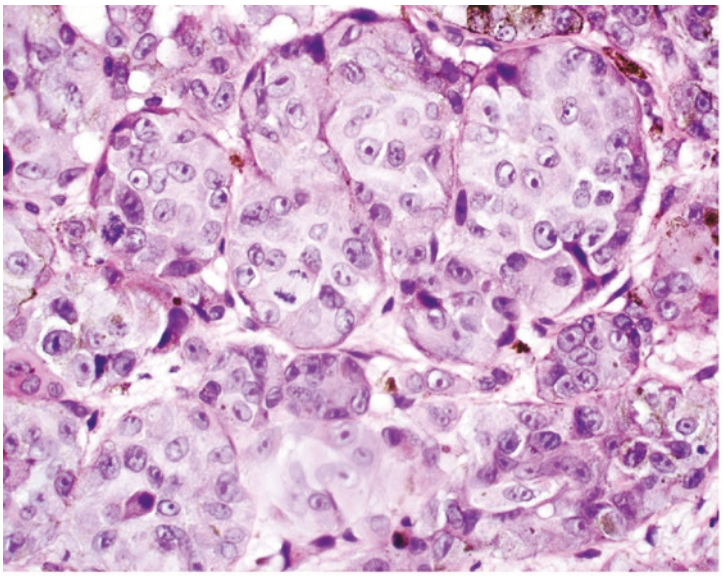
- Nuclear features of **BCC** with cytoplasmic features of **SCC**

18-5



18-6

Melanoma



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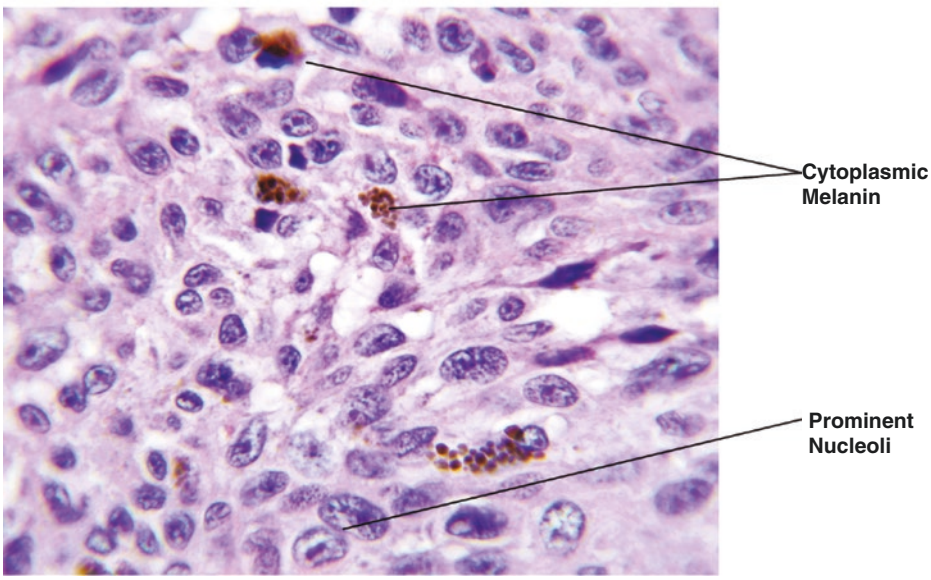

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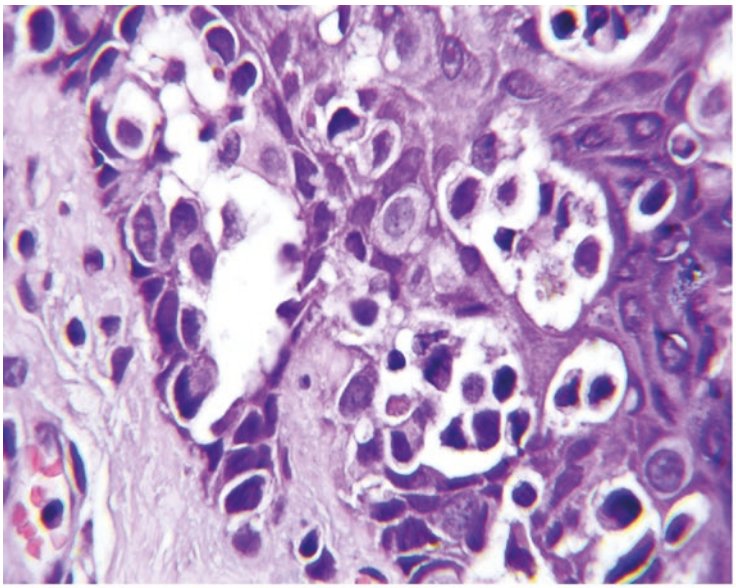
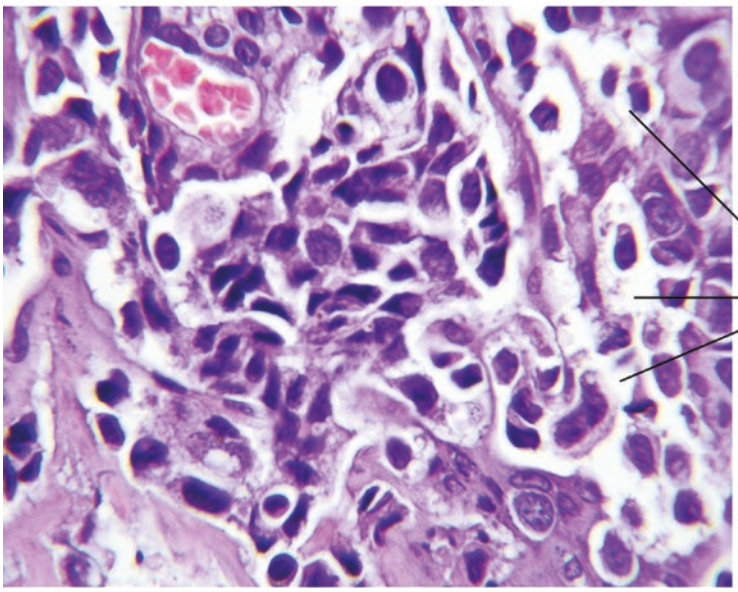
Paget's Disease



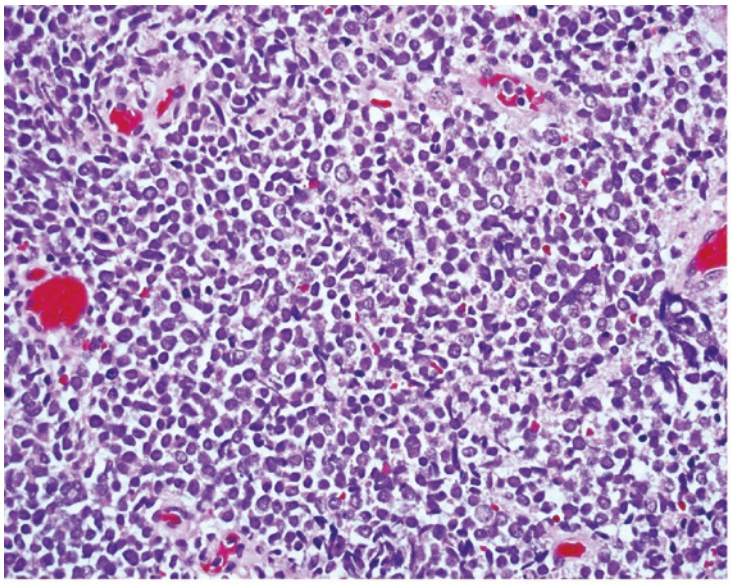
Note: Nested and single clear cells throughout epithelium

18-9



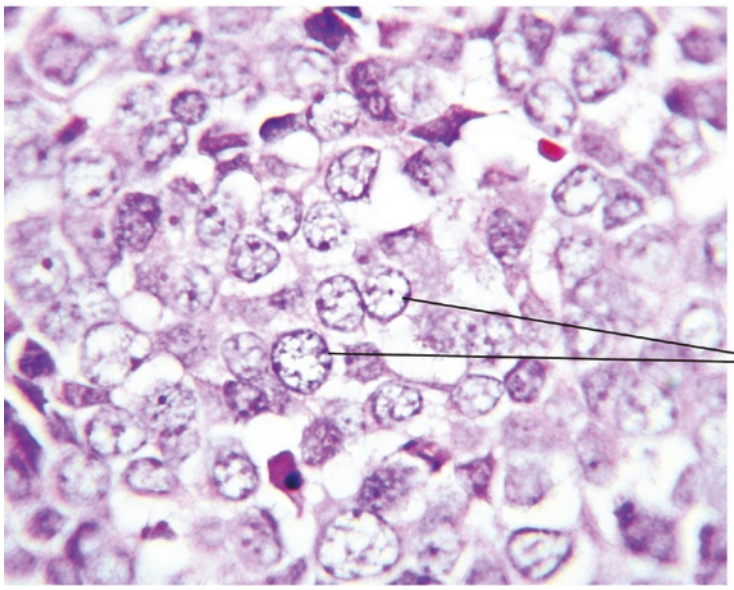
18-10

Merkel Cell Carcinoma



- Dyshesive uniform cell population with scant cytoplasm

18-11

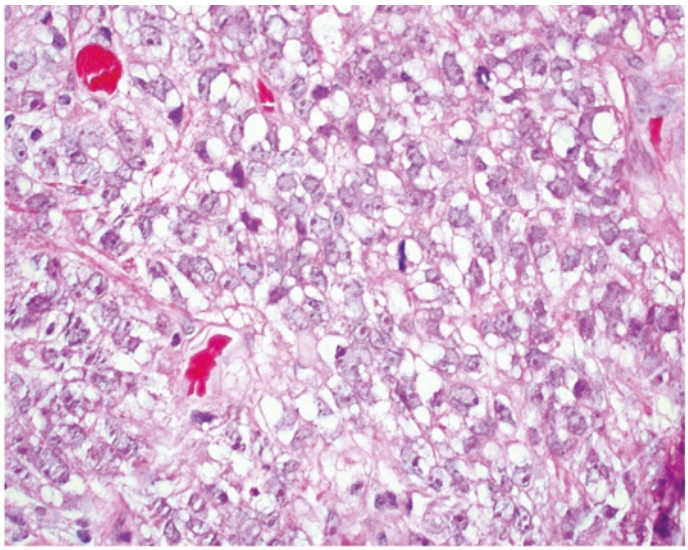


Note: Stippled nuclear chromatin

Scant cytoplasm with fusion of nuclear membranes

18-12

Sebaceous Carcinoma



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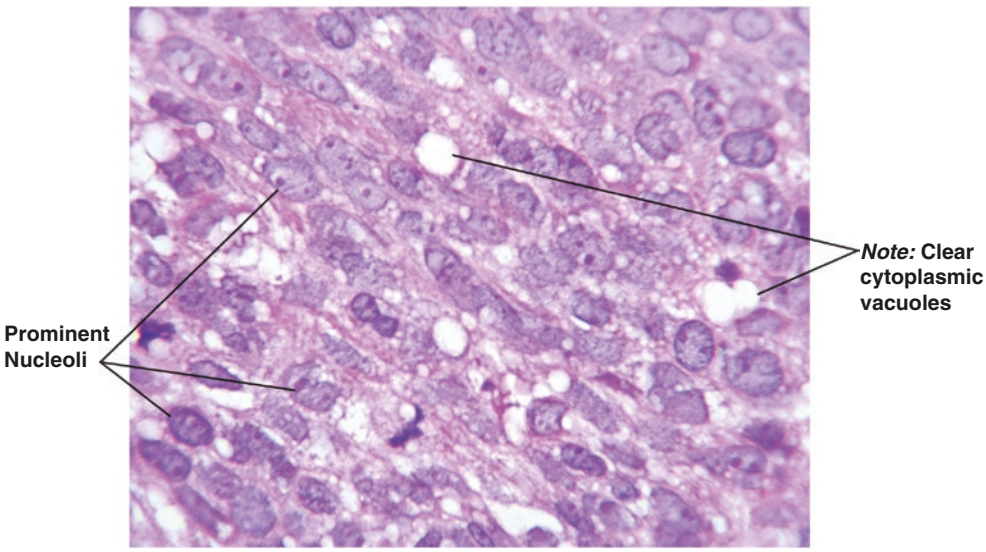

18-14

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Immunohistochemistry Applications

19

Basil S. Cherpelis, L. Frank Glass, John R. Hamill Jr., and Neil Alan Fenske

Immunohistochemistry can be applied judiciously in the delineation of tumoral histiogenesis and the extent of lesional involvement in frozen section pathology. Among the more important immunostains and applications are the use of the MART-1 stain in melanoma, cytokeratin immunostain in cutaneous epithelial malignancy and Ber-EP4 in basal cell carcinoma.

In certain situations, identification of residual tumor may be difficult, which may increase the risk of recurrence. These situations include poorly differentiated tumor cells, tumor cells among a dense inflammatory infiltrate and tumors with perineural invasion. It is now possible to employ immunoperoxidase techniques in frozen sections as an adjunct to routine hematoxylin and eosin (H&E) staining to aid in ensuring negative margins, decreasing the likelihood of leaving behind residual tumor and therefore decreasing the likelihood of tumor recurrance. Traditionally, immunostains have taken at least one hour to process, but recent advances by Cherpelis et al. have shortened the time to less than twenty minutes for both MART-1 and cytokeratin immunostains. This shortened time greatly increases the efficiency and practicality of using immunostains in the frozen section laboratory.

Mohs surgeons have traditionally been wary of treating melanoma. The difficulty lies in freeze artifact produced on frozen sections which makes it difficult to distinguish between melanocytes and keratinocytes. Immunostains may be used as an adjunct to identify melanocytes on frozen sections in the treatment of melanoma in situ. MART-1 is currently considered the most useful. Proper immunostaining, however, requires expertise in preparation and in interpretation. Frozen sections must be cut very thin; no more than 4 μc. The dermasurgeon must be adept at recognizing the histopathologic features of melanoma as well as being able to distinguish melanoma from chronic sun damage.

While the recognition of BCC and SCC in hematolylin and eosin (H&E) stained frozen sections is uncomplicated in most instances, exceptions occur. For example, dense inflammation can obscure tumor cells hidden within the lymphocytic infiltrate. Sclerosing morphology or perineural disease are other characteristics that may substantially increase the difficulty in detecting tumor. The use of immunostaining in Mohs surgery for NMSC has been examined and found useful in these situations. A broad spectrum anticytokeratin (AE1/AE3) is generally employed and can detect both squamous cell and basal cell carcinoma. A monoclonal antibody against human epithelial antigen (Ber-EP4) recognizes an epithelial glycoprotein antigen that occurs in various tissues. In the skin, it occurs in cells of adnexal structures in normal skin as well as BCCs, but does not stain keratinocytes or SCCs. Staining for Ber-EP4 may prove useful in

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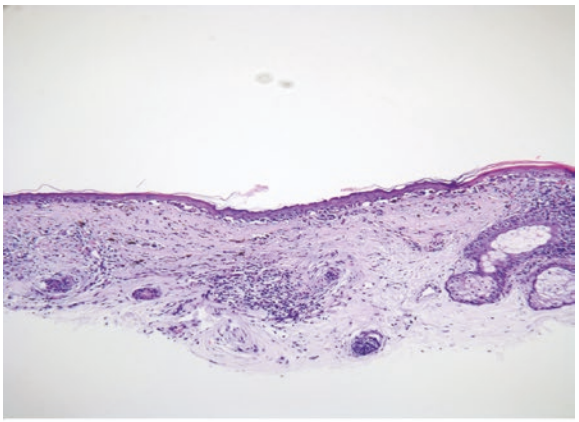
https://doi.org/10.1007/978-3-319-74847-4_19

differentiating BCC from hair follicles in frozen sections, as Ber-EP4 is generally absent from hair follicles except for the base of some hair bulbs.

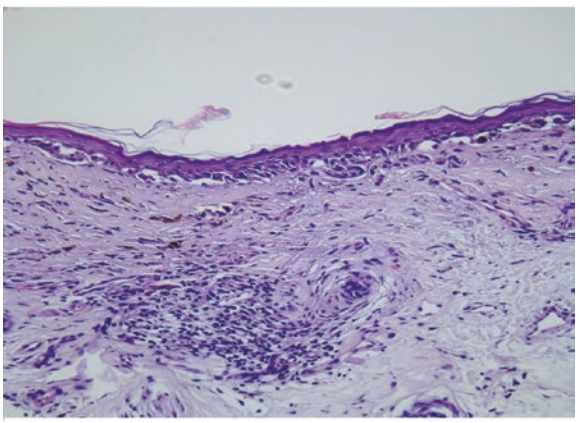
Other stains the Mohs surgeon may find useful include Oil Red O for sebaceous carcinoma, CK 7 or CEA for extramammary Paget's disease, and CK 20 for merkel cell carcinoma. The rarity of these tumors and cost of immunostains generally limits the practicality of these more esoteric stains, and "slow" Mohs with permanent sections is often employed to treat these tumors.

Melanoma in Situ



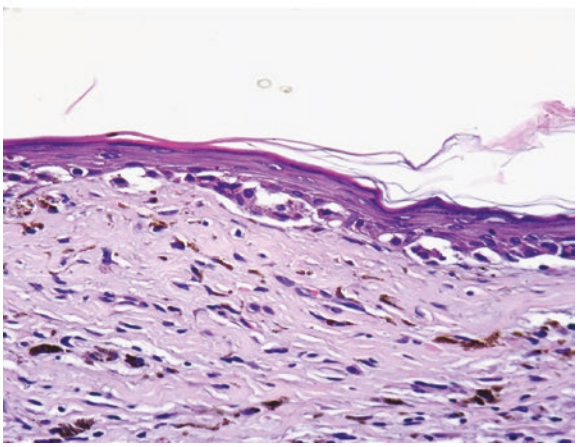
LOW 19-1

- Increased number of poorly circumscribed atypical melanocytes



MEDIUM 19-2

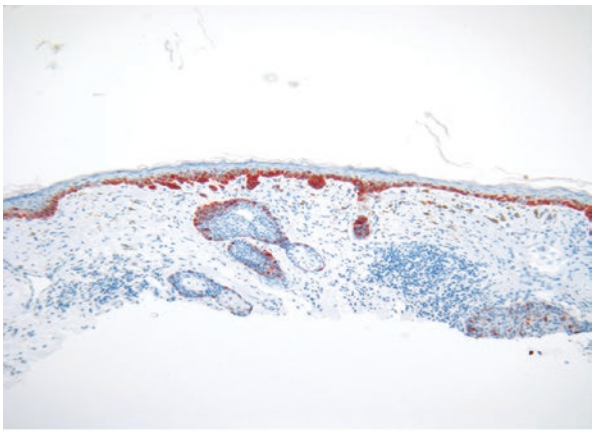
- Increased number of atypical melanocytes and haphazard arrangement of nests



HIGH 19-3

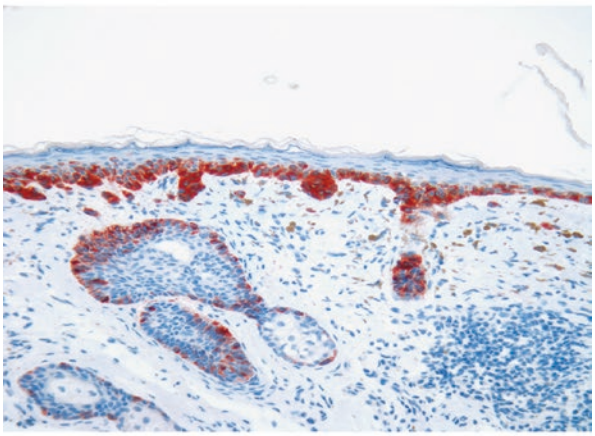
- Detail of irregularity of nests and atypical melanocytes

Melanoma in Situ Mart-1 Immunostain



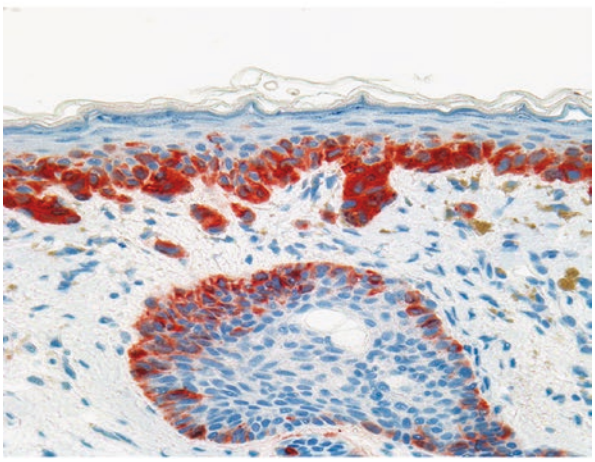
LOW 19-4

- Increased number of atypical melanocytes along DE junction



MEDIUM 19-5

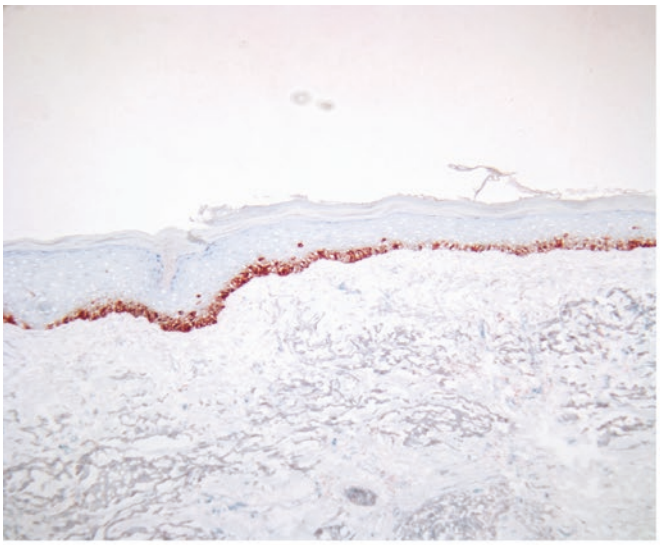
- Increased number of atypical melanocytes
- Pagetoid spread
- Extension down follicles



HIGH 19-6

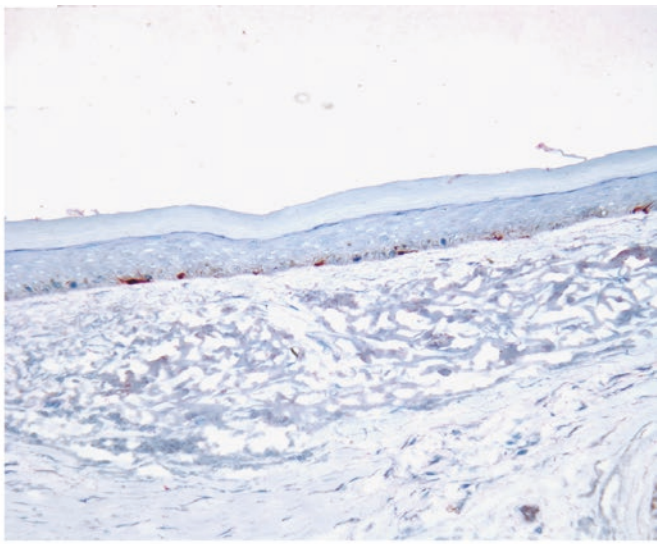
- Detail of irregular of nests and pagetoid spread

Melanoma in Situ vs. Chronic Sun Damaged Skin



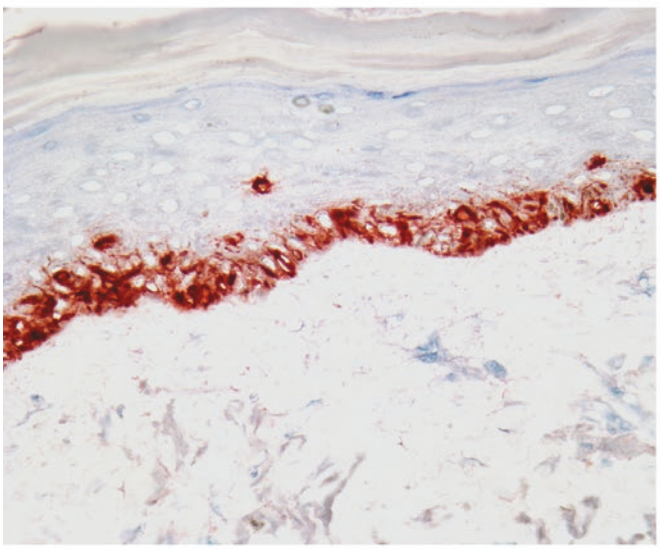
19-7

- Increased number of confluent atypical melanocytes
- Pagetoid spread of melanocytes



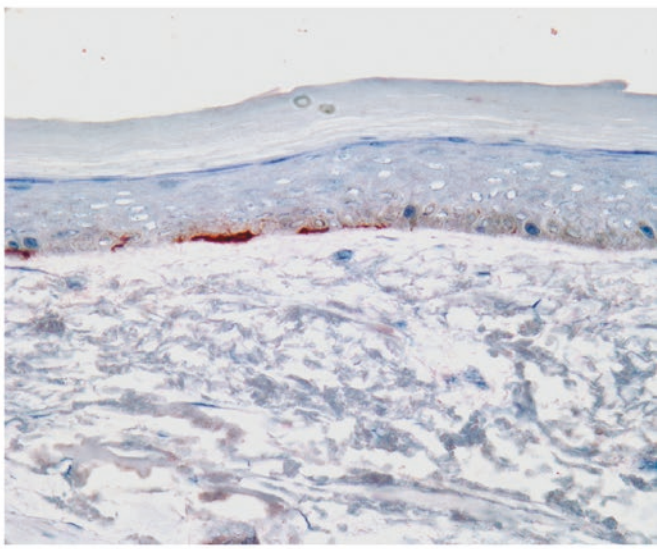
19-8

- No confluence of melanocytes
- No pagetoid spread
- No nesting of melanocytes



19-9

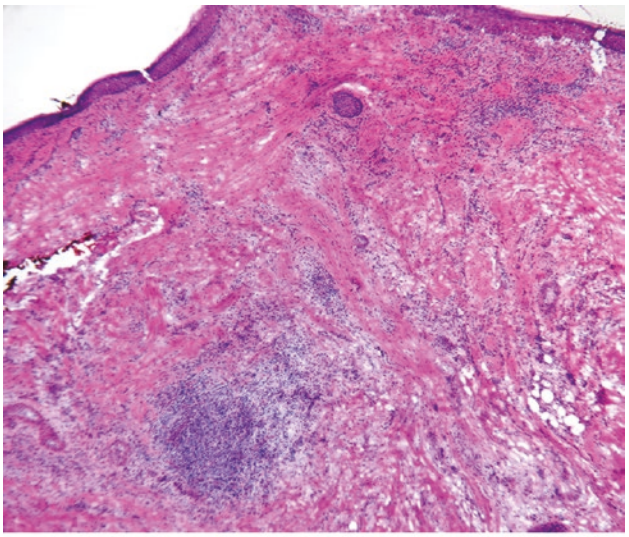
- Increased number of confluent atypical melanocytes



19-10

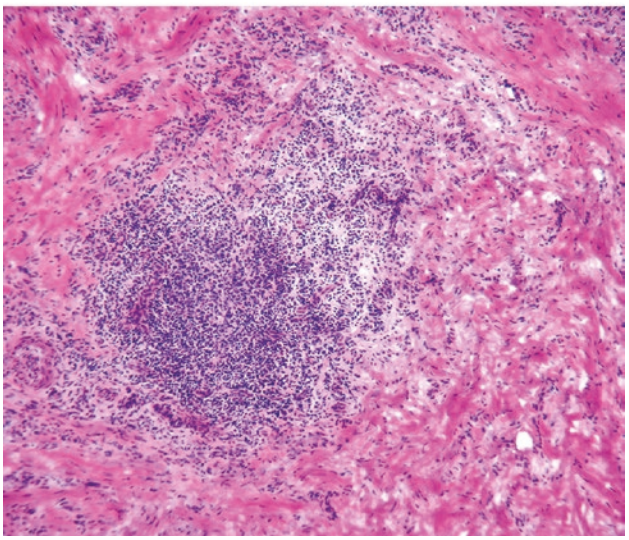
- No confluence of melanocytes
- No pagetoid spread
- No nesting of melanocytes

Cytokeratin Immunostain



LOW 19-11

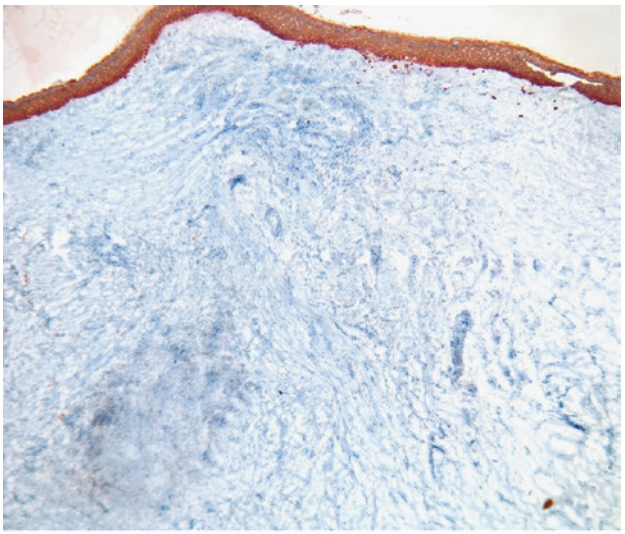
- H&E staining of Mohs margin reveals a focus of dense inflammation that could mask tumor cells



HIGH 19-12

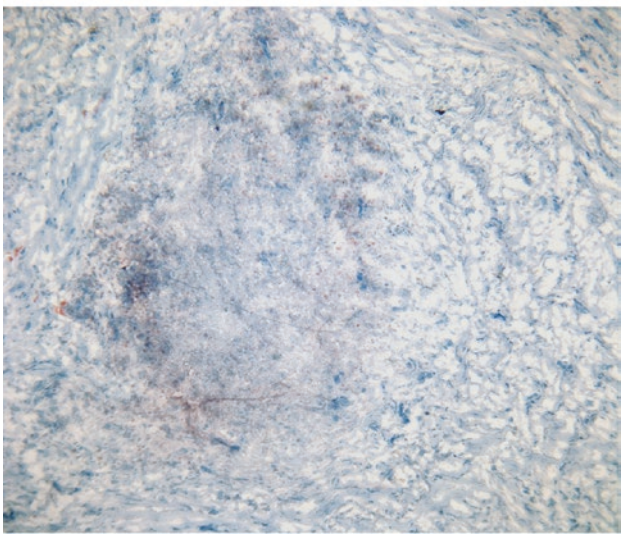
- Higher power view of the dense inflammatory infiltrate

Cytokeratin Immunostain



19-13

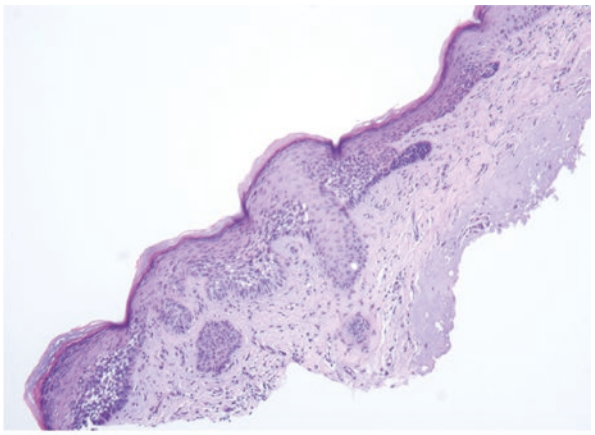
- CK immunostain of same area confirms that no tumor is present within the area



19-14

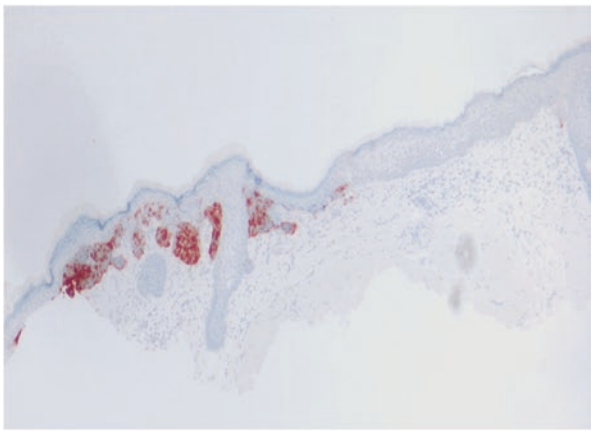
- Higher power view of C with lack of residual BCC, sparing the need for additional layer of tissue to be taken

BER-EP4 Immunostain



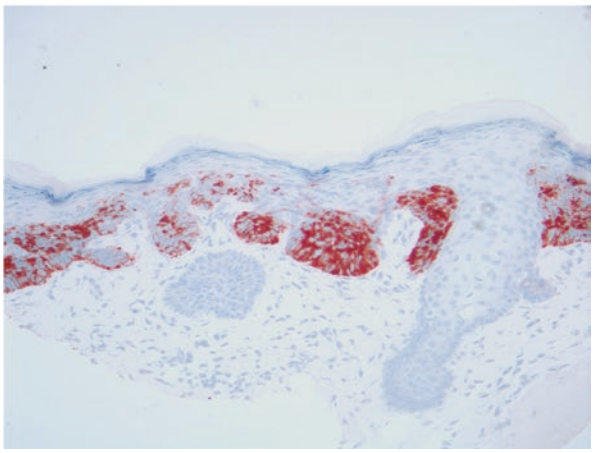
LOW 19-15

- Sometimes it may be difficult to distinguish between BCC and hair follicles



MEDIUM 19-16

- Ber-EP4 immunostain can help differentiate BCC from hair follicle



HIGH 19-17

- Higher power view demonstrating uptake of stain by BCC while avoiding uptake of normal follicle

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Histotechnique and Staining Troubleshooting

20

John R. Hamill Jr. and Stephen Spencer

This chapter deals with identification, distinction and correction of most of the potential sources of error introduced in the rendering of frozen section tissue sections.

"*Your successss rate as a physician interpreting frozen sections cannot be any better than the quality of the slides.*"

~ James Spencer, M.D.
July 2008

Successful identification of potential slide processing error requires discernment of key microscopic details that serve as reproducible changes signifying any number of pitfalls or missteps that may occur prior to, during or after slide preparation. This chapter is divided into four sections including in vivo, preparation, cutting and staining error. Pre-analytic error entails pathologic conditions that existed within the tissue prior to removal from the patient that can be confused with meaningful pathologic entities or post-procedural error and includes such changes as foreign body granuloma and retained suture. Preparation error entails procedural problems not associated with cutting and/or staining such as the recognition of inadequate or excessive use of mounting medium. Cutting problems involve the recognition of knife blade inadequacy or the inadequate use of embedding medium among other problems frequently encountered. Finally, staining challenges due to deviation from suggested staining protocol need to be recognized. Each section includes an index of key microscopic features typically seen with each particular source of error, a differential diagnosis to entertain and solution(s) to consider. Unfortunately, many of the observed microscopic deviations can be produced by alternative sources of error rendering solution problematic for even the most experienced Moh's surgeons. This challenge may be further exacerbated by the presence of more than one source of error or entail a single source of error masquerading in a variety of histologic guise. Attention to microscopic detail, elimination of confounding sources of error and scrutiny of the slide preparation process by the supervising physician, however, will usually permit its successful identification.

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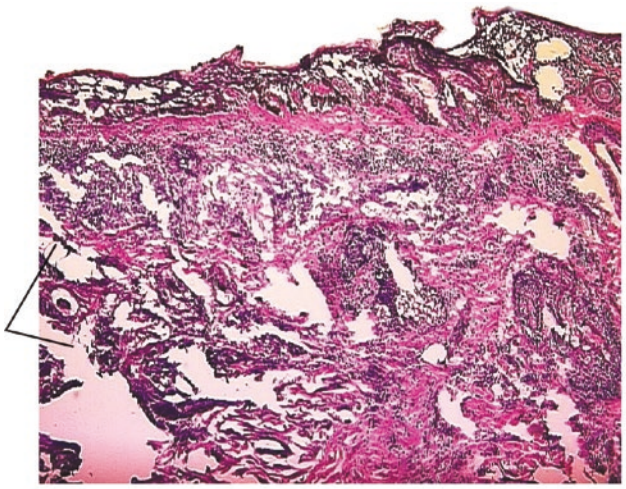
https://doi.org/10.1007/978-3-319-74847-4_20

In Vivo Challenges

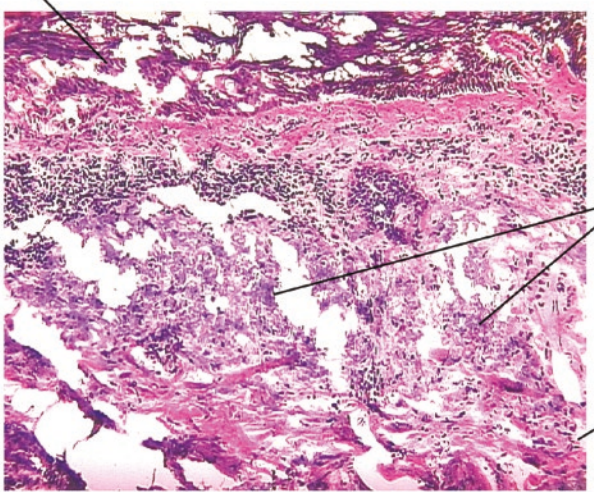
CAUTERY EFFECT-*LOW*



20-1

MOTH-EATEN EPIDERMIS

CAUTERY EFFECT-*HIGH*



PRESERVED SOLAR ELASTOSIS

CONGEALED COLLAGEN

20-2

MICROSCOPIC FEATURES

Blurry tissue sections
Increased holes in tissue
Preserved solar elastosis
Congealed collagen fibers
“Moth-eaten” epidermis

DDX

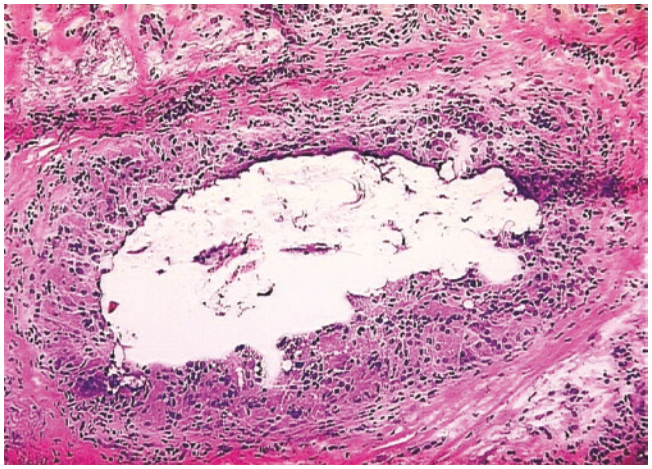
Inadequate O.C.T./over freezing
Dull blade

SOLUTION

Avoid or minimize electro-cautery

In Vivo Challenges

FOREIGN BODY GRANULOMA



20-3

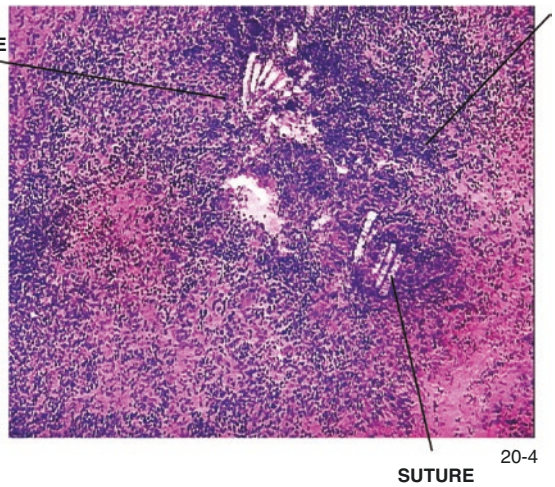
MICROSCOPIC FEATURES
Palisaded histiocytes
Irregular outline
Clear/depleted center

DDX
Dislodged calcium or bone
Dull blade effect

SOLUTION
Review history

In Vivo Challenges

RETAINED SUTURE



20-4

MICROSCOPIC FEATURES

Laminar array of bright/light objects
Often associated with chronic inflammation including lymphocytes and histiocytes (granuloma)

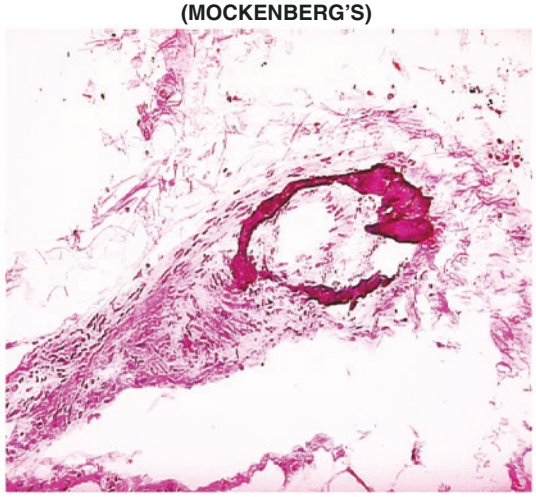
DDX

Keratin fragments
Calcium oxalate crystals
Calcium phosphate crystals
Uric acid crystals

SOLUTION

Review history

CALCIFIED BLOOD VESSEL (MOCKENBERG'S)



20-5

MICROSCOPIC FEATURES

Circular array of dark purple corresponding to vessel outline

DDX

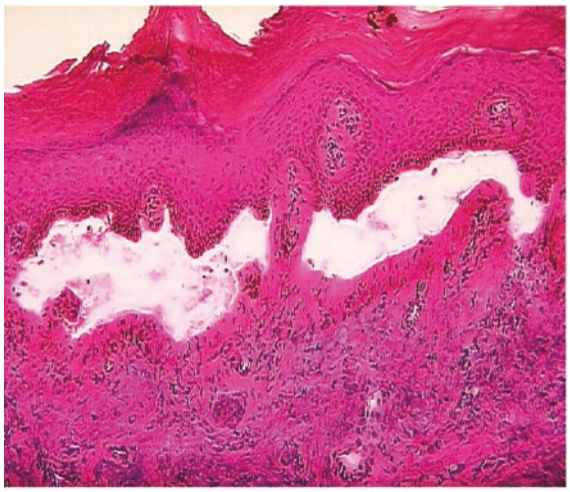
Dystrophic calcification
Calciphylaxis

SOLUTION

Clinical correlation

In Vivo Challenges

TISSUE TEAR/RIP DUE TO SCAR



20-6

MICROSCOPIC FEATURES

Jagged defect in tissue at the epidermal/dermal junction
Dermal fibroplasia corresponding to scar tissue

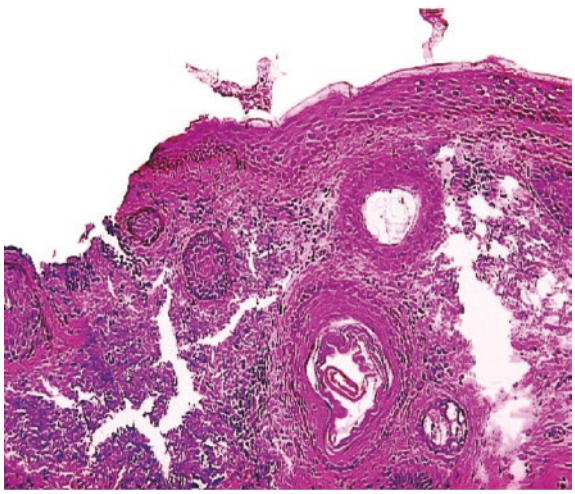
DDX

Dull blade/knick
Retained hard object at point of tear

SOLUTION

Review history

CLEFTED SOLAR ELASTOSIS



20-7

MICROSCOPIC FEATURES

Irregular amorphous grey-colored superficial dermal aggregates
Irregular clefts within solar elastosis

DDX

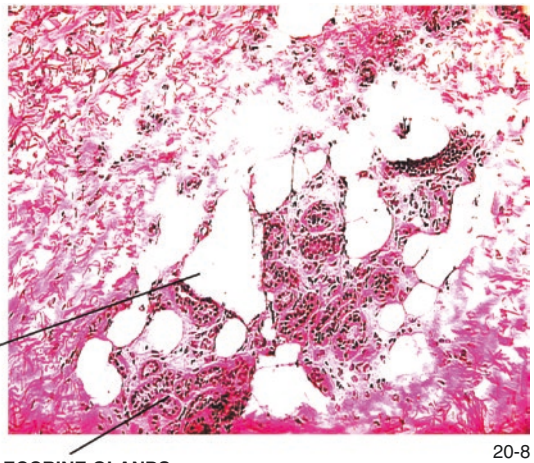
Dislodged calcium or bone
Dull blade effect

SOLUTION

Clinical correlation

Preparation Challenges

NORMAL FAT AROUND ECCRINE



20-8

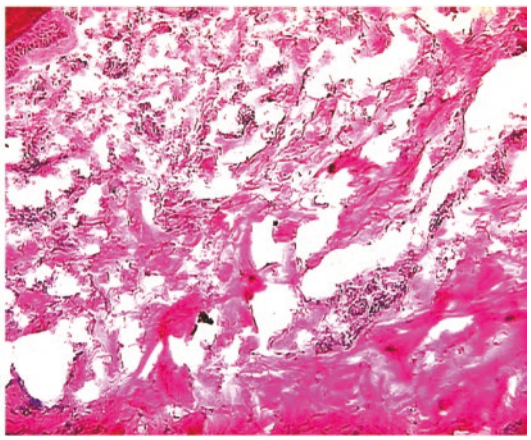
MICROSCOPIC FEATURES

Irregular holes in tissue plane
NO discernable outlines

DDX

Air coverslip vacuoles
Normal adipose tissue
Dislodged hard (i.e., bone/calcium) fragments

TISSUE VACUOLES



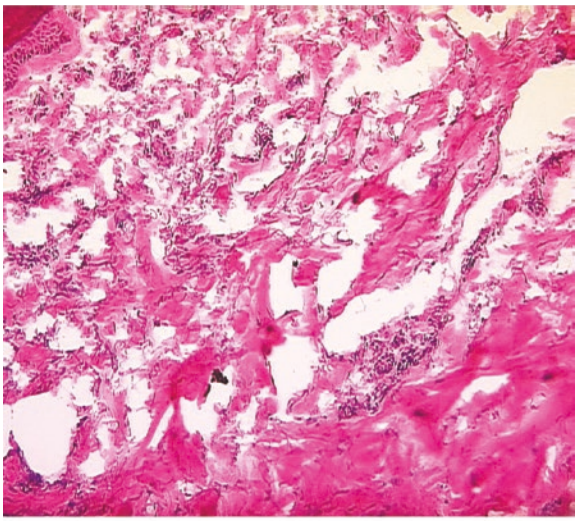
20-9

SOLUTION

Consider sharper blade
Consider planning block (rubbing specimen on smooth surface) prior to cutting

Preparation Challenges

TISSUE VACOULES



20-10

MICROSCOPIC FEATURES

Irregular holes in tissue plane
No discernable outlines

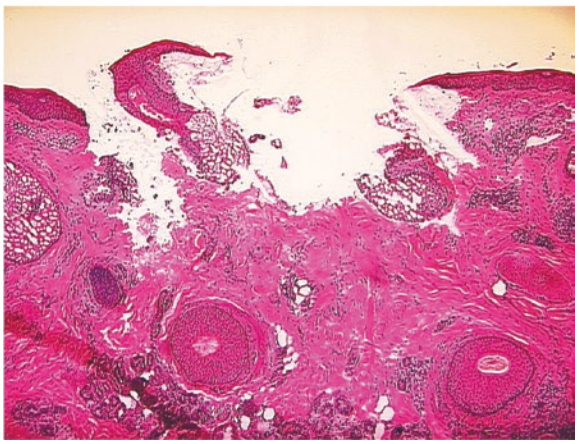
DDX

Air coverslip vacuoles
Normal adipose tissue
Dislodged hard (i.e., bone/calcium) fragments

SOLUTION

Consider sharper blade
Consider planning block (rubbing specimen on smooth surface) prior to cutting

JAGGED SURFACE DEFECT DUE TO DULL BLADE



20-11

MICROSCOPIC FEATURES

Irregular outlined hole in sections often with broader at epithelial surface

DDX

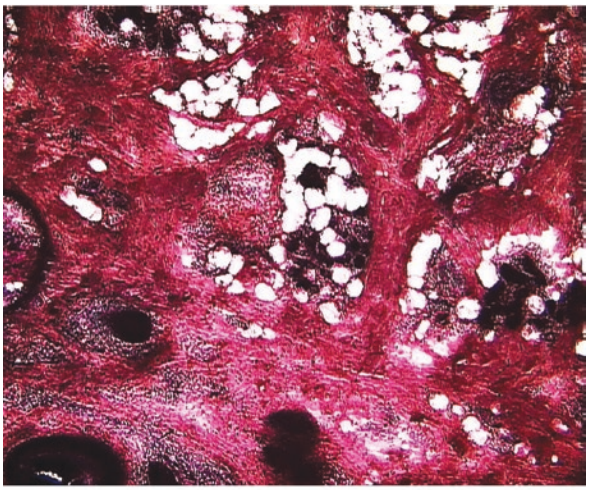
Surgical (scalpel) knick
Tissue section at angle

SOLUTION

Sharper blade
Less thick sections
Ensure tissue is flat prior to embedding

Preparation Challenges

INADEQUATE COVERSLIPING



20-12

MICROSCOPIC FEATURES

Dull-appearing tissue sections
Appears out of focus

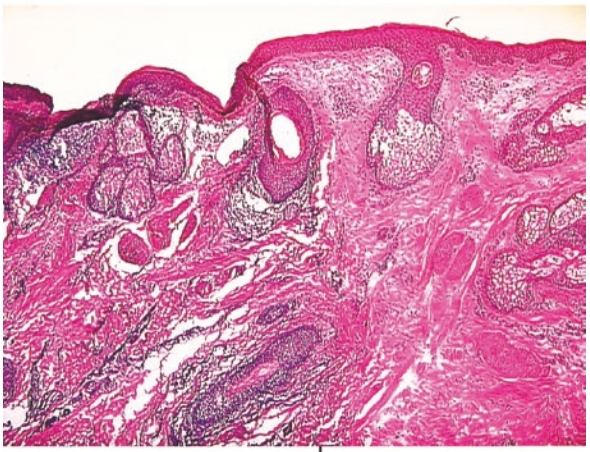
DDX

Thick sections
Excessive drying/storage of old slides
Light exposure

SOLUTION

Ensure coverslip is placed upon tissue
Store slides in cool dark place

TISSUE FREEZE



20-13

DEMARCATION POINT

MICROSCOPIC FEATURES

Abrupt loss of microscopic detail
Often seen at edge of specimen

DDX

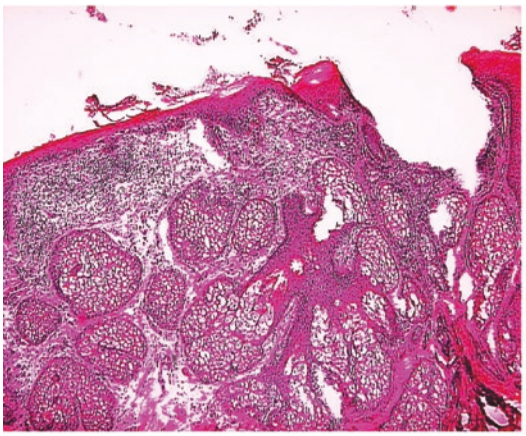
Cautery Effect

SOLUTION

Ensure adequate O.C.T. application
Avoid over freezing
Avoid quick-freeze solution

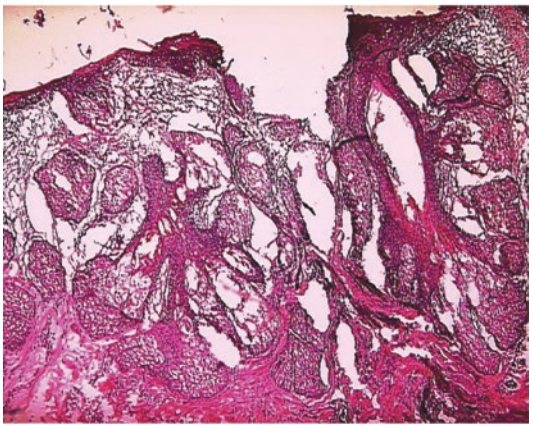
Preparation Challenges

NORMAL SECTION



20-14

EXCESSIVE QUICK FREEZE APPLIED



20-15

MICROSCOPIC FEATURES

Focal loss of microscopic detail
Excess tissue holes

DDX

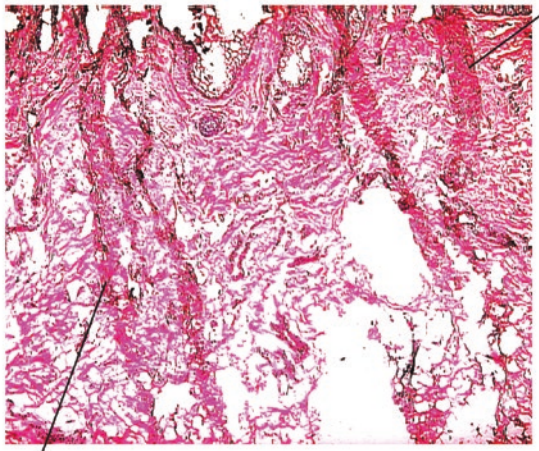
Sections too thick
Dull blade
Inadequate O.C.T.

SOLUTION

Avoid spray or quick freeze *applied* with application

Cutting Challenges

TISSUE FOLDS (VENETIAN BLIND)



20-16

MICROSCOPIC FEATURES

Linear densities running perpendicular to horizontal axis

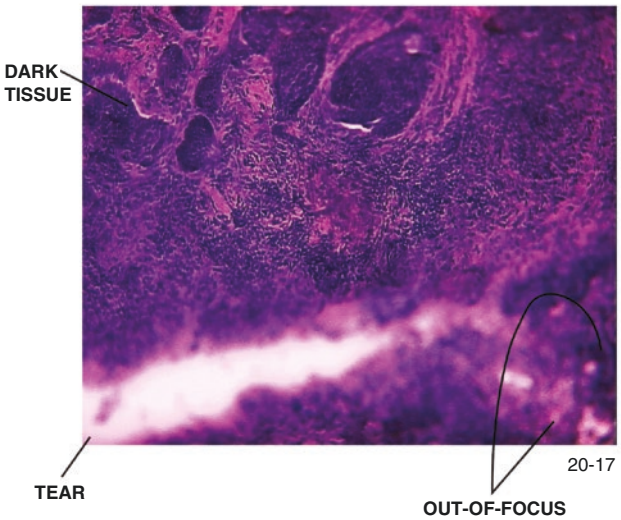
DDX

NONE

SOLUTION

Gentle traction on sections with brush
Colder cryostat temperature

TOO THICK SECTIONING



20-17

MICROSCOPIC FEATURES

Darkly stained tissue
Tissue tears
Out of focus portions

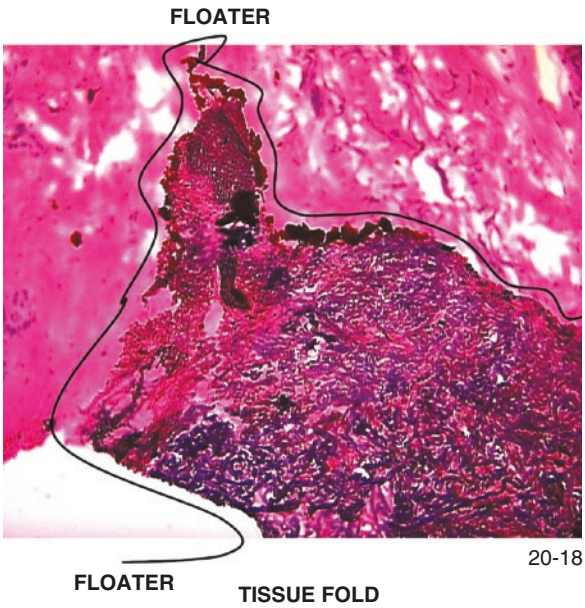
DDX

Dull blade
Overstaining with hematoxylin

SOLUTION

Cut at 4-5 *um* thick sections

Cutting Challenges



20-18

MICROSCOPIC FEATURES

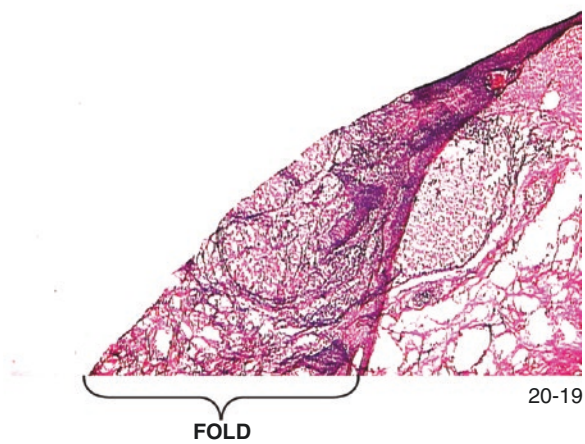
Out of focus portion
Irregular outlining of darker specimen
Often seen at edge of section

DDX

Tear/rip of section

SOLUTION

Ensure sharp blade
Avoid introduction of extraneous tissue
Clean blade/cryostat cover plate



20-19

MICROSCOPIC FEATURES

Outlined darker area
Loss of resolution in darker area

DDX

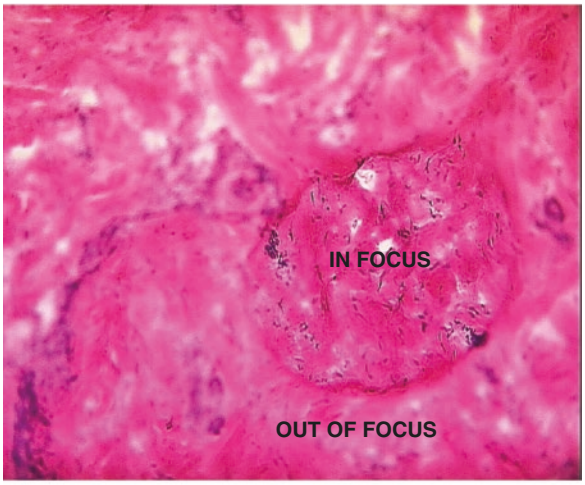
Floater

SOLUTION

Improper adjustment of anti-roll bar on cryostat
Sections too thick

Cutting Challenges

OUT-OF-FOCUS TISSUE



20-20

MICROSCOPIC FEATURES

Portion of tissue out of focus

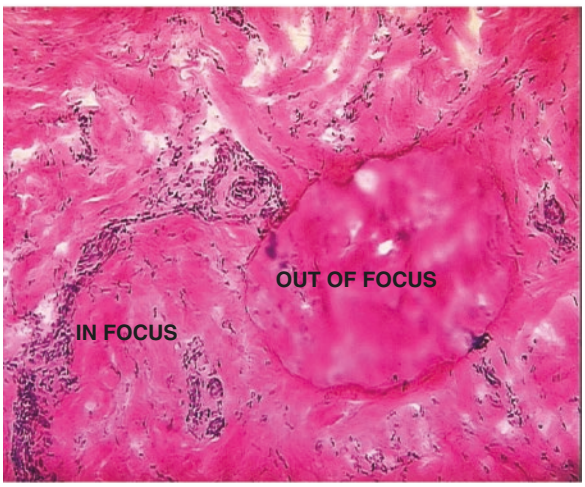
DDX

Dirty microscope lenses or moisture on coverslip/lenses

SOLUTION

Clean lenses and coverslip
Check to ensure sections not too thick
Check quality of blade

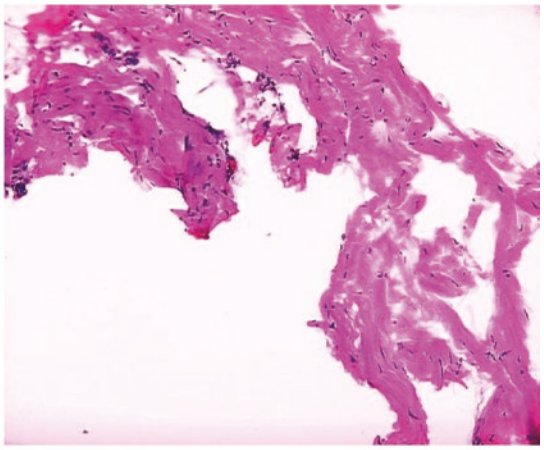
OUT-OF-FOCUS TISSUE



20-21

Cutting Challenges

LOSS OF ADIPOSE TISSUE DUE TO WARM TEMPERATURE



20-22

MICROSCOPIC FEATURES

Large holes where subcutaneous fat should be

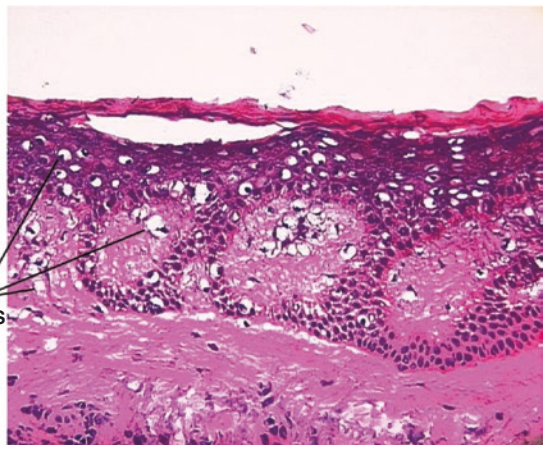
DDX

Sections too thick
Dull blade

SOLUTION

Specimen is too warm
Blade is to warm

VACUOLAR CHANGE OF EPITHELIUM WITH FREEZING



20-23

MICROSCOPIC FEATURES

Vacuole (holes) in cytoplasm of keratinocytes
Rest of specimen appears normal

DDX

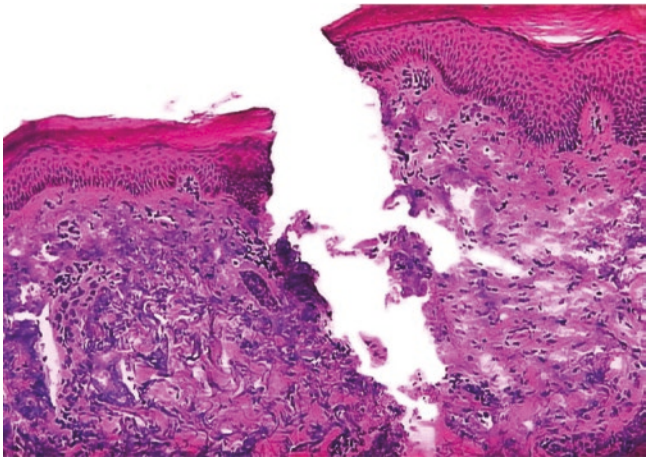
Verruca plana
Squamous carcinoma-in-situ

SOLUTION

Avoid excessive freezing
Ensure adequate O.C.T.

Cutting Challenges

TISSUE TEAR/RIP DUE TO BLADE KNICK



20-24

MICROSCOPIC FEATURES

Jagged defect in tissue
Dagger-like morphology with axis running perpendicular to epithelium

DDX

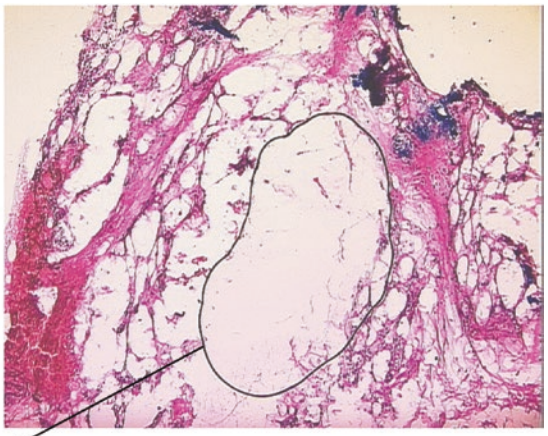
Dull blade
Return hard object at less point of tear

SOLUTION

Ensure adequate blade

Staining Challenges

AIR UNDER COVERSLIP



20-25

MICROSCOPIC FEATURES

Irregular rounded structure
Sharp boundaries

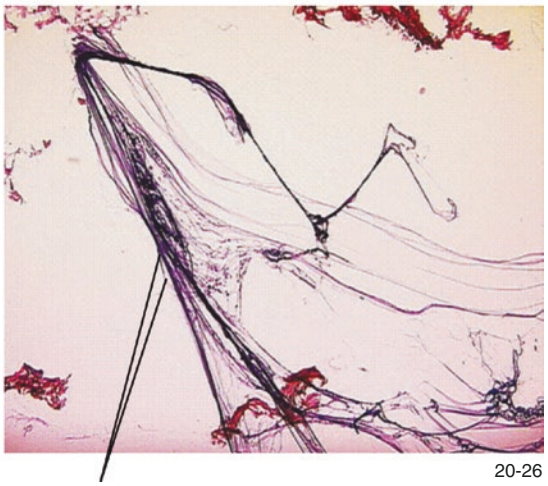
DDX

Tissue vacuoles

SOLUTION

Press coverslip more firmly
Consider additional mounting medium

HEMATOXYLIN PRECIPITATES



20-26

MICROSCOPIC FEATURES

Cobweb-like purple streaks

DDX

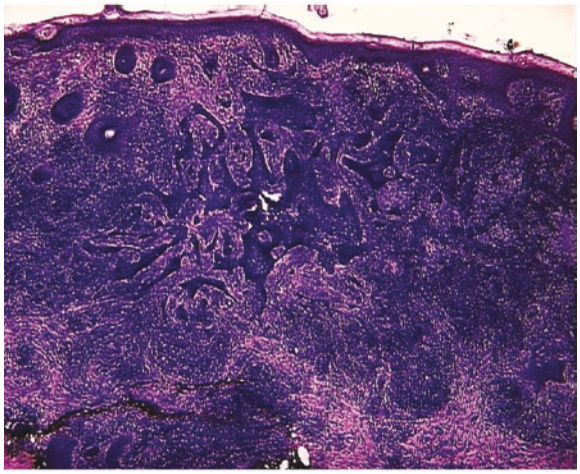
Extraneous tissue/debris

SOLUTION

Utilize fresh hematoxylin (<24 hours)
Ensure filtration if hematoxylin is to be used for greater than one day

Staining Challenges

TOO LITTLE EOSIN/INADEQUATE EOSIN STAIN



20-27

MICROSCOPIC FEATURES

Darkly stained tissue

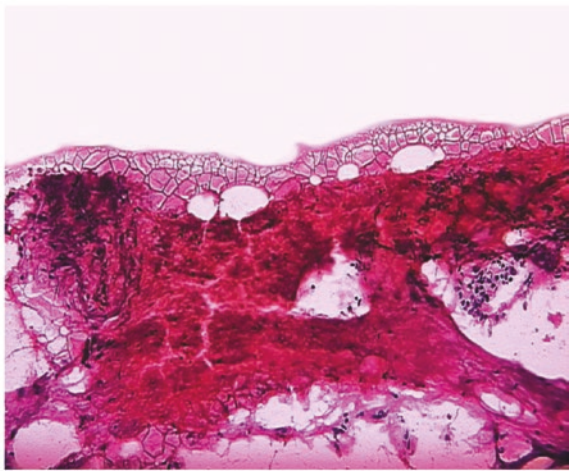
DDX

Too much hematoxylin

SOLUTION

Ensure adequate staining time
(30 seconds) with freshly prepared eosin

TOO MUCH EOSIN



20-28

MICROSCOPIC FEATURES

Pink stained tissue
"Eosin bleed" (cracked fringes of tissue)

DDX

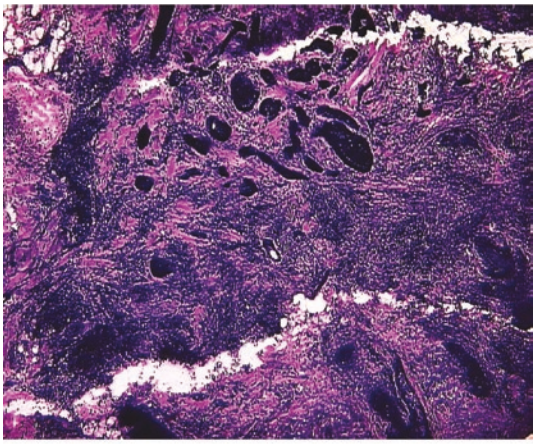
Inadequate hematoxylin

SOLUTION

Avoid excessive staining with eosin
(> 30 seconds)

Staining Challenges

TOO MUCH HEMATOXYLIN



20-29

MICROSCOPIC FEATURES

Darkly stained tissue sections

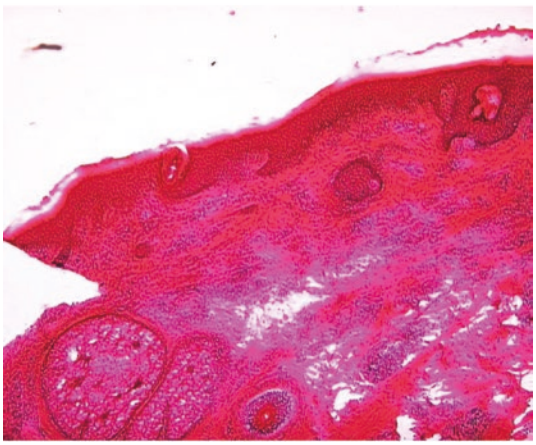
DDX

Too little eosin

SOLUTION

Avoid excessive hematoxylin staining
(> 30 seconds)

TOO LITTLE HEMATOXYLIN



20-30

MICROSCOPIC FEATURES

Pink stained tissue
No “eosin bleed”

DDX

Too much eosin

SOLUTION

Ensure adequate hematoxylin exposure
(30 seconds)
Ensure that bluing agent (ammonia)
is used and solution is fresh (<than 24 hours)

Quick-Reference Trouble Shooting Guide

1. **Tissue too dark**	♦ Too much hematoxylin ♦ Inadequate eosin ♦ Sections too thick ♦ Loss of coverslip	♦ Check hematoxylin staining step ♦ Check eosin staining step ♦ Check thickness setting
2. **Tissue too pink**	♦ Too much eosin ♦ Inadequate hematoxylin ♦ Inadequate ammonia	♦ Check eosin staining step ♦ Check for fresh ammonia
3. **Tissue holes**	♦ Dull blade ♦ Inadequate freezing ♦ Tissue cut too thick	♦ Check blade ♦ Check cryostat temperature ♦ Check thickness setting
4. **Tissue folds**	♦ Inadequate traction of tissue with application to slide ♦ Inadequate freezing	♦ Review technique ♦ Check cryostat temperature
5. **Tissue focally out-of-focus**	♦ Dirty lenses ♦ Sections too thick	♦ Clean lenses, slides and coverslip ♦ Check thickness setting
6. **Tissue tear**	♦ Dull blade ♦ Retained hard object in tissue	♦ Check blade ♦ Review history

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Part V

Mohs Clinicopathologic Self-Test Series

A Painful Perineural Infiltrate

21

Rebecca S. Thornhill and Tyler Scott

A 64-year-old Caucasian man with a history of multiple skin cancers, including a recent diagnosis of microinvasive well-differentiated squamous cell carcinoma (SCC) of the lower lip, presented for Mohs surgery. He complained of dysesthesia, including tingling of the lip. Physical examination yielded a crusted papule at the vermillion border that was clinically attributed to previous biopsy site changes. Histologic sections showed the following findings.

The correct diagnosis is:

(a) Leprosy
(b) Herpes labialis
(c) Melkersson-Rosenthal syndrome
(d) Bell palsy

The correct answer is (b), herpes labialis. At low power histologic sections yielded (Fig. 21.1) a papillomatous configured exophytic squamous neoplasm with a dense lymphocytic infiltrate and underlying rounded lymphoid infiltrates. Higher power examination (Fig. 21.2) of the mucosa yielded dyskeratosis, with viral cytopathic changes consisting of molded, marginated, and multinucleated nuclei. The submucosa disclosed a predominantly lymphoid infiltrate seen extending around the perineural space and surrounding small caliber nerves (Fig. 21.3).

In this case the herpes labialis was masquerading as an SCC-associated lymphocytic perineuritis. This is the typical presentation of herpes simplex virus/varicella zoster virus (HSV/VZV) double-stranded DNA herpes virus cytopathic effect. Despite the history of SCC and the presence of chronic lymphoid infiltrates, the microscopist should be aware of other entities that are capable of showing chronic perineuritis in addition to invasive SCC. Chronic perineuritis can be seen in the context of leprosy, HSV/VZV infection, and chronic inflammatory conditions such as Bell palsy and the Melkersson-Rosenthal syndrome (MRS) [1–3]. These histologic features notwithstanding, particular attention should be paid to the clinical history and other accompanying histo-

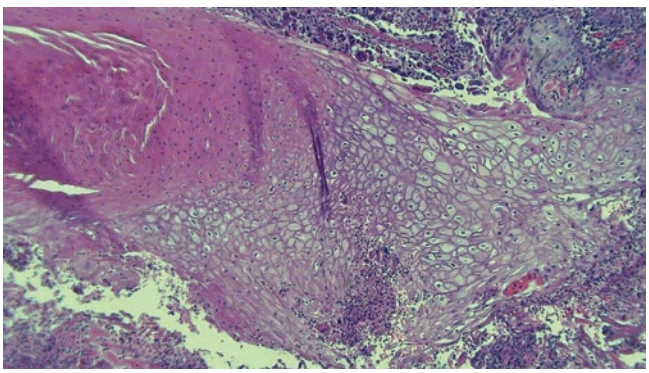

Fig. 21.1 Papillomatous squamous neoplasm

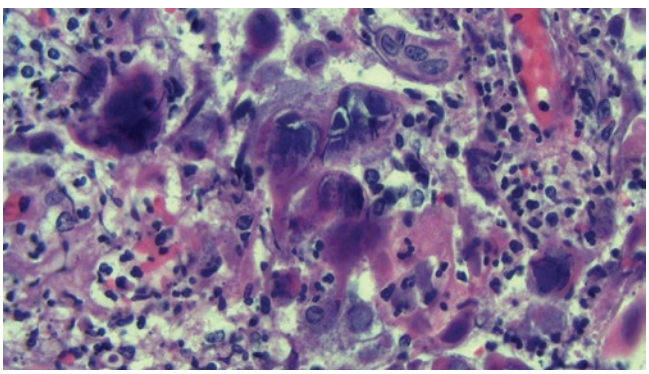

Fig. 21.2 Dyskeratotic mucosa with molded, marginated, and multinucleated nuclei

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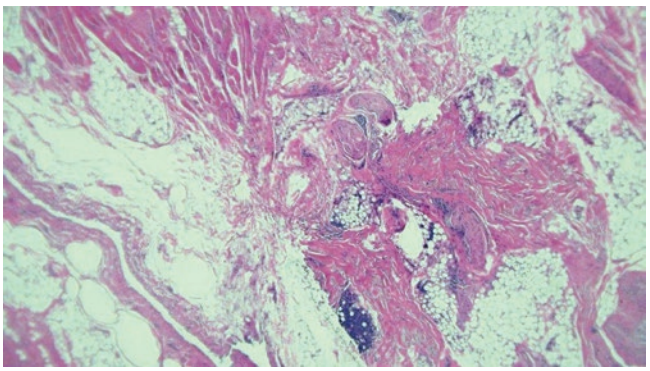

Fig. 21.3 Lymphoid infiltrate extending around perineural space

logic subtleties such as histiocytes within the perineurium of leprosy and the blood vessels of Bell palsy and MRS.

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae,* an intracytoplasmic parasite of macrophages and Schwann cells that mainly targets the skin and peripheral nerves. Microscopically perineural inflammation may exhibit a linear pattern as it follows the nerve. The clinical triad of MRS consists of orofacial edema (particularly of one or both lips), facial palsy, and a fissured tongue. The disease may manifest in individuals with all three clinical findings or be limited to facial palsy with or without an antecedent viral prodrome in the context of Bell palsy. Histopathologic evaluation of MRS traditionally reveals noncaseating granulomatous inflammation with lymphangitis, while Bell palsy demonstrates lymphocytic neuritis.

Cutaneous HSV and VZV are common viral infections of the skin and mucosal surfaces. After primary infection, the virus is believed to establish latency in the dorsal root ganglia. When reactivated, it travels along sensory nerves to cause skin disease, usually described as grouped vesicles on an erythematous base. While the classic clinical presentation would be dissimilar to that of mucosal SCC, the dysesthesia and pain that might accompany this infection would be related to perineural extension of the SCC or other malignancy. Without immunohistochemical, serologic, or molecular methodology, the histologic features of HSV1/2and VZV are indistinguishable. The non-DNA viral exanthems produce changes of ballooning and reticular degeneration. However, viral cytopathic features, specifically the three M's (molded, marginated, and multinucleated [nuclei], are not seen. Interestingly, the other herpes viruses, such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV), do not produce epithelial changes as described. Rather, CMV preferentially produces cytopathic effects in vascular endothelial cells, whereas EBV affects the lymphocytes themselves.

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A Painful Subcutaneous Nodule

22

Rebecca S. Thornhill and Nicole Asher

A 68-year-old man with a remote history of squamous cell carcinoma (SCC) involving the submental area presented with a slowly growing painful 2-cm subcutaneous nodule. Low-power examination (Fig. 22.1) yielded an ill-circumscribed deep dermal/subcutaneous lesion. At intermediate power (Fig. 22.2), a dense scar is seen approximating spindled cellular areas that at high-power examination (Fig. 22.3) yielded a wavy orientation typical of nerve tissue. The nerves are infiltrated and surrounded by densely chromatic cohesive cells, and in some areas dyskeratosis can be seen. Discernible inflammation is not identified.

The correct diagnosis is:

(a) Adenoid cystic carcinoma
(b) Basal cell carcinoma
(c) Melanoma
(d) Atypical fibroxanthoma
(e) Squamous cell carcinoma
(f) Epithelial sheath neuroma

The correct answer is (e), squamous cell carcinoma. The histopathology describes perineural tumoral infiltrates (PNI), which can be defined as tumor cells within any of the three layers of the nerve sheath or tumor foci outside of the nerve with involvement of at least 33% of the nerve's circumference [1]. While SCC is the most common cutaneous malignancy to show PNI, malignant adnexal neoplasms, including adenoid cystic carcinoma, show the greatest propensity for PNI. Basal cell carcinoma (BCC), melanoma, and atypical fibroxanthoma (AFX) may also occasionally show PNI. While chronic (lymphocytic) perineural inflammation can be a helpful clue suggestive of PNI, its absence should not eliminate the possibility of PNI, particularly if clinical symptoms suggest otherwise.

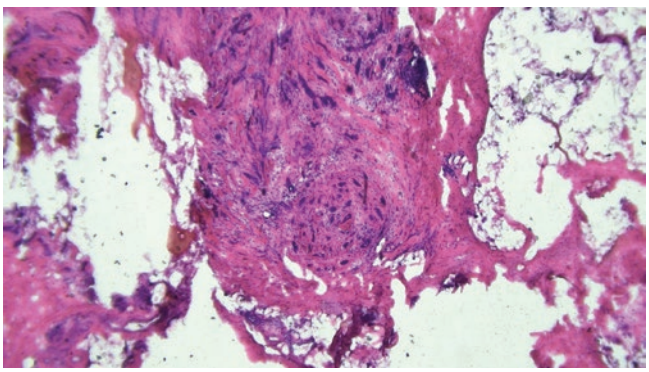

Fig. 22.1 Deep dermal lesion

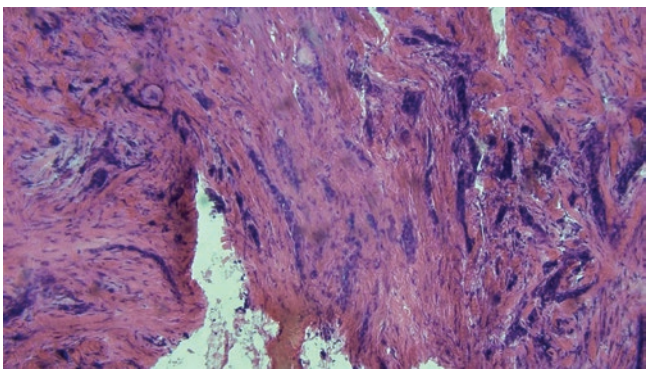

Fig. 22.2 Dense scar approximating spindled cellular areas

Interestingly, there are several benign entities capable of showing perineural extension, such as congenital melanocytic nevi and hemangioma. However, three additional benign cutaneous entities may pose a significant histologic uncertainty with PNI. Peritumoral fibrosis (PF) is the most

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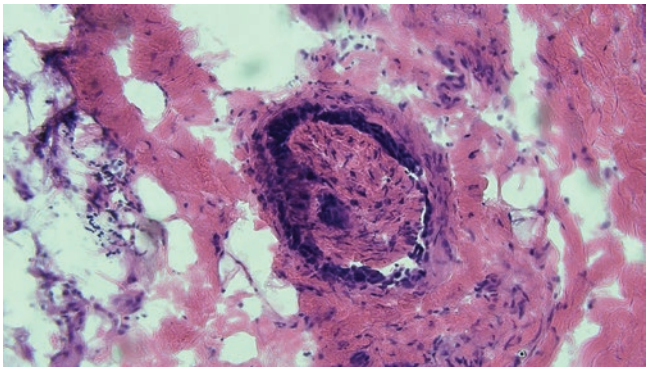

Fig. 22.3 Nerve tissue surrounded by hyperchromatic and dyskeratotic cells

common of these entities, occurring in 6% of BCCs and 5% of SCCs and showing characteristic concentric fibroplasia around non-neural–associated tumoral deposits [2]. Strands of fibrous tissue may be difficult to distinguish from nerve tissue without the aid of additional stains, such as S100. The highest incidence of PF was noticed in recurrent BCC. Concurrent microscopic PNI was seen in 29% of BCCs with PF and in 50% of SCCs with PF. PF is a more sensitive marker of coexisting PNI than perineural inflammation. The authors caution all to perform a thorough search for microscopic PNI when PF is present [2].

Epithelial sheath neuroma (ESN), although rare, shows a histopathologic appearance so striking that it is possible to have a case misdiagnosed as PNI. Characteristic proliferation of large nerve trunks is seen in the upper dermis, ensheathed by benign squamous epithelium. Microscopically, ESN multifocally permeates the reticular dermis as discrete nerve complexes consisting of enveloping perineural mantles composed of mature, sometimes keratinizing squamous epithelium and central nerve trunks. The surrounding dermis shows delicate fibroplasia containing mucin and a mild inflammatory cell infiltrate composed of lymphocytes with few plasma cells. There is no associated in situ or invasive carcinoma and no changes from previous surgery. The overall effect is striking, with an obvious resemblance to PNI associated with SCC. The cytopathology of ESN is indistinguishable from that of PNI in an SCC. The overall architecture showing large involved nerve trunks high in the reticular dermis is diagnostic of ESN.

Re-excision perineural invasion (RPI) refers to the observation of mature benign squamous epithelium in the perineural spaces of cutaneous nerves in re-excision specimens [3]. Diagnostic criteria include the absence of perineural spread beyond the immediate previous biopsy site, benign appearance of the perineural epithelial cells in contrast to the appearance of the original tumor, absence of residual epithelial tumor in the vicinity of the involved perineurium, and eccrine ducts adjacent to the involved nerve.

On occasion, regenerating nerves in a healing surgical wound may reveal prominent proliferation of the perineurium [4]. Histologically, concentric rings of bland spindle-shaped cells envelop a nerve adjacent to scarring and reparation from the prior surgery. This reparative process may mimic microscopic PNI, especially in the context of a previous malignancy. The nature of the condition can be confirmed by showing negative Immunohistochemical staining in the spindle cells for S100 and cytokeratins but positive staining with epithelial membrane antigen, as would be seen in normal perineural cells.

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Basaloid Lesion

23

Tyler Scott and Nicole Asher

A 54-year-old woman with a family history of basal cell carcinoma (BCC) and a personal history of multiple BCCs that had been removed since she was the age of 21 presented for follow-up of a recently diagnosed nodular BCC of the cheek. Physical examination of the area revealed healed biopsy site changes. However, the patient insisted upon rebiopsy to exclude basal cell recurrence. The new biopsy revealed the following microscopic findings.

The correct diagnosis is:

(a) BCC
(b) Trichoepithelioma variant of trichoblastoma
(c) Basaloid follicular hamartoma masquerading as BCC
(d) Pilomatricoma

The correct answer is (c), basaloid follicular hamartoma (BFH) masquerading as BCC. Low-power examination yielded epidermal atrophy with sebaceous hyperplasia and multiple discontinuous basaloid follicular neoplasms (Fig. 23.1) seen in close continuity with overlying epithelium. Intermediate-power showed an arborizing composite architecture that despite its overall symmetry yielded basophilic staining strands, solid areas, and cystic formation (Fig. 23.2) devoid of discernible myxoid or eosinophilic peritumoral stroma. High-power examination of the cystic areas reflected hair shafts (Fig. 23.3).

BFH was first described by Mehregan as consisting of multiple localized and systemized benign follicular neoplasms. It was later expanded to include familial, linear, syndromic, and incidentally noted cases that shared a common histology and molecular constituency involving the sonic hedgehog pathway [1]. The principal histologic features are solid strands and branching cords of undifferentiated basaloid cells, often connected to or closely associated with existing follicles and intervening fibrous stroma [2]. These structures are seen to be confined to the superficial dermis, lack the typical peripheral palisade and retraction artifact of BCC cell carcinoma, and are symmetrically oriented in both the vertical and horizontal planes [3].

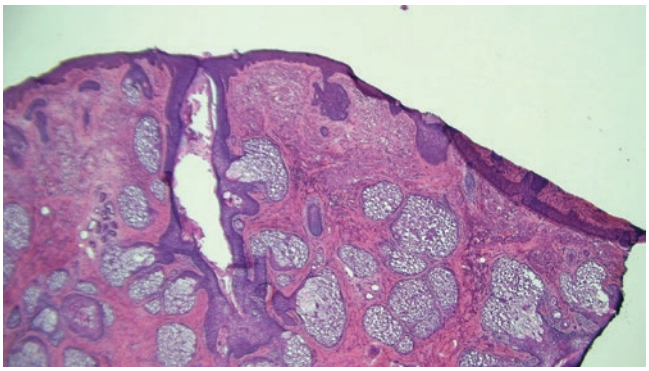

Fig. 23.1 Epidermal atrophy with sebaceous hyperplasia and basaloid neoplasms

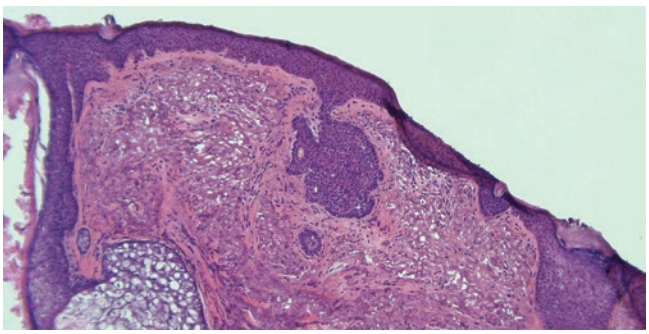

Fig. 23.2 Arborizing composite architecture with basophilic staining strands, solid areas, and cystic formation

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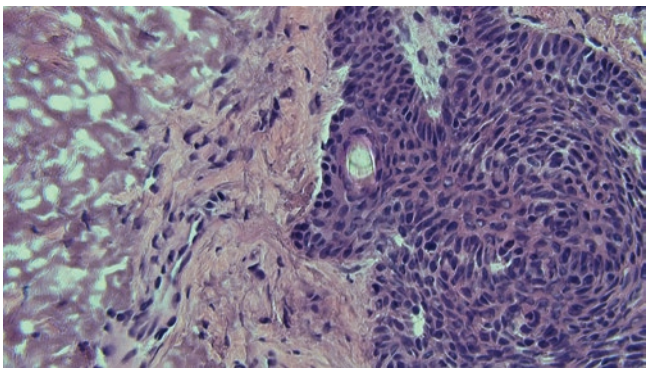

Fig. 23.3 Hair shafts within cystic areas

The differential diagnosis would include conventional BCC, particularly of the infundibulocystic type, and benign trichoblastoma, particularly of the trichoepithelioma type. Infundibulocystic BCC is a rare variant of BCC that like BFH is most commonly encountered on the face. It is similarly diminutive, well-circumscribed within the dermis, and consists of anastomosing cords with little intervening stroma. However, this neoplasm is characterized by numerous keratinizing cystic structures often containing melanin pigment. Furthermore, infundibulocystic BCC shares with conventional forms of BCC an asymmetric overall architecture, an increased number of mitotic and apoptotic figures within the basaloid foci, and the absence of hair shafts within the cystic areas. Hair shafts can be more readily identified by polaroscopy or by lowering the substage condenser of the examiner's microscope.

Like BFH and infundibulocystic BCC, the trichoepithelioma variant of trichoblastoma is most often encountered on the face, but it tends to be a larger neoplasm often extending into the lower regions of the dermis. Its principal distinction lies in the appreciation of its distinctive peritumoral stroma, which unlike conventional BCC is cellular, is eosinophilic staining, and is equal in composition to the basaloid foci [4]. The overall disposition, although symmetric, is horizontally oriented and is often associated with an intradermal nevus and accompanying micro cysts that may elicit a giant cell reaction and dystrophic calcification.

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Rapidly Growing Hemorrhagic Papule

24

Rebecca S. Thornhill and Nicole Asher

A 49-year-old Caucasian woman with a history of invasive well-differentiated squamous cell carcinoma (SCC) showing perineural invasion that was diagnosed by biopsy 2 weeks prior presented for Mohs micrographic surgery of the cheek. First-stage sections yielded changes of wound repair at low power (Fig. 24.1), and a vaguely rounded structure surrounded by chronic inflammation (including primarily lymphocytes) was noted in the deeper dermis. At intermediate-power examination (Fig. 24.2), the rounded silhouette of the structure shows a complex internal structure consisting of multiple fenestrated foci. At high-power examination (Fig. 24.3), the channels contain hyperchromatic nuclei that are in turn surrounded by and invested in a myxoid stroma.

The correct diagnosis is:

(a) Organizing thrombus
(b) Intravascular extension of carcinoma
(c) Chronic perineuritis
(d) Merkel cell carcinoma

The correct answer is (a), organizing thrombus. The predisposing conditions to arterial or venous thrombosis, termed the Virchow triad, include (1) preexisting trauma, including the previous biopsy in this instance; (2) an intrinsic hypercoagulable state, for example, factor V Leiden syndrome or disseminated carcinomatosis; and (3) hemodynamic changes, for example, venous stasis or turbulent arterial flow. Reliable features of thrombosis are time-dependent and consist of perivascular pathology and intravascular changes. The perivascular alterations, as seen in this example, would include chronic inflammation with lymphocytes and accompanying scarring of the dermis and necrosis of subcutaneous fat. Successful recognition of the process is dependent upon identification of a vessel, with key attributes including the rounded or oval-shaped silhouette and symmetry in two planes typical of vessels, either arterial or venous. Arterial structures endowed with elastic lamina (Fig. 24.4) can be seen as the festooned eosinophilic structure in the mid-portion of the vessel wall as well as thick smooth muscle media and mixed

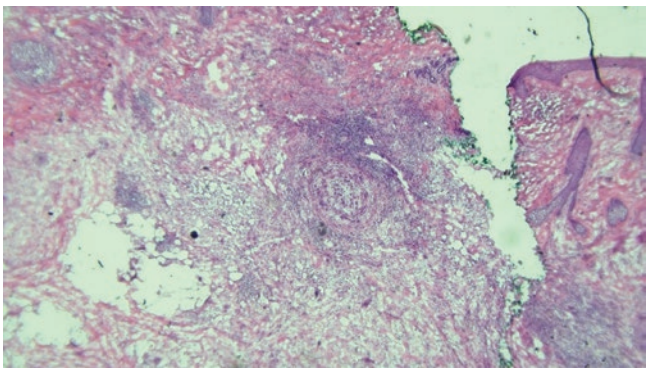

Fig. 24.1 Rounded structure with lymphocytic inflammation

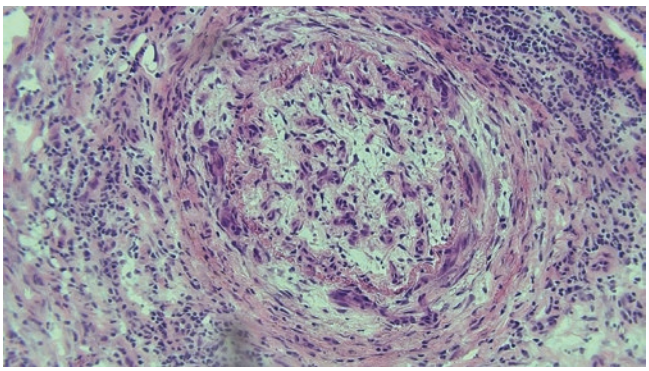

Fig. 24.2 Rounded silhouette with multiple fenestrated foci

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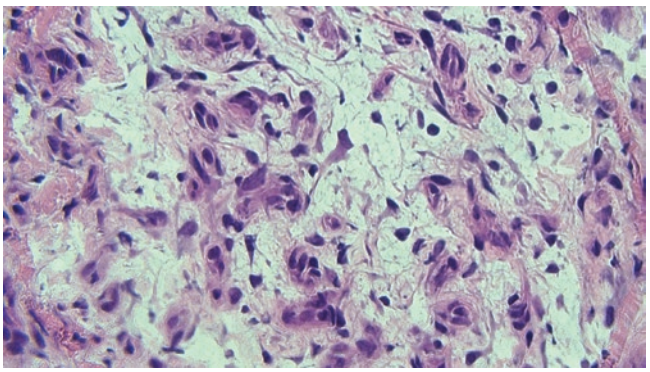

Fig. 24.3 Channels of hyperchromatic nuclei in myxoid stroma

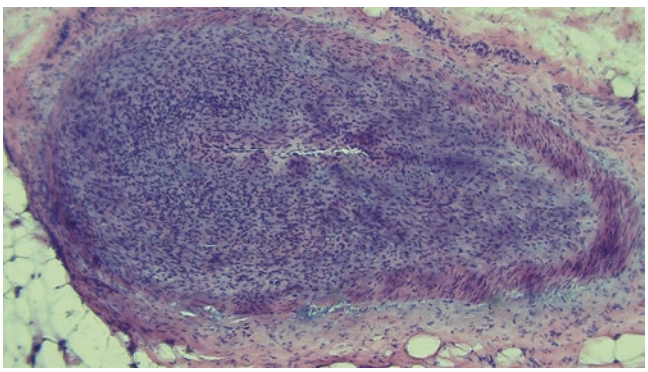

Fig. 24.4 Arterial structures endowed with elastic lamina

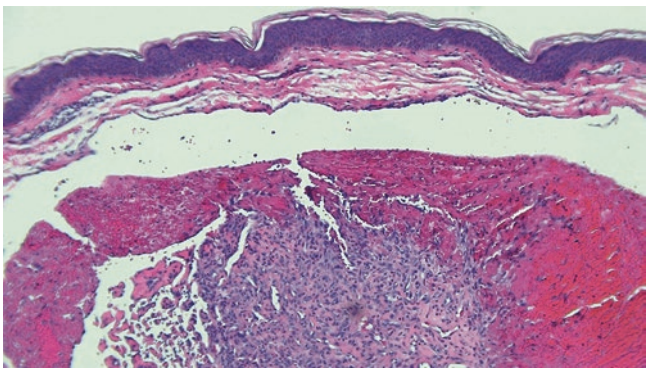

Fig. 24.5 Chronic organizing thrombus yielding recanalized endothelia and a myxoid stroma

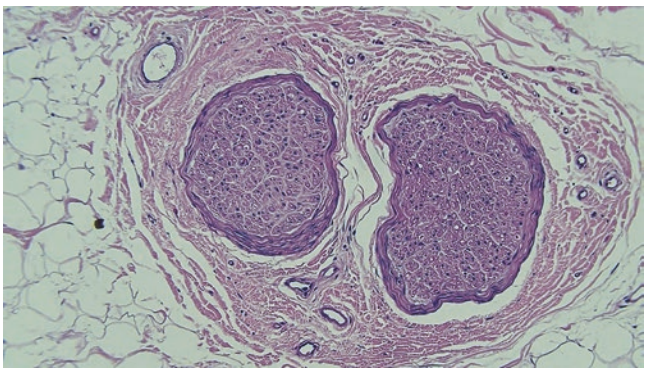

Fig. 24.6 Bundled myelinated axons with investing Schwann cells surrounded by endoneurium that form fascicles surrounded by specialized perineural fibrocytes, forming the perineurium. These are associated collectively with other nerve fascicles and vessels surrounded by an epineurium

adventitia typical of an arterial or muscular medium-sized artery. The intravascular pathology varies and is time-dependent, with acute thrombosis yielding alternating fibrinous strands, erythrocytes (lines of Zahn), and chronic organizing thrombi with varying numbers of recanalized endothelia and a myxoid stroma (Fig. 24.5). Discontinuous endothelial-lined sinusoids in the Masson's lesion may also be found [1, 2]. At high-power examination, close attention should be paid to the key microanatomic attributes of the vascular wall and the presence of endothelial-lined vascular channels, which in some examples will contain erythrocytes as well.

The histologic differential diagnosis includes intravascular extension of carcinoma and perineural pathologies, including chronic perineuritis. Like blood vessels, larger caliber nerves are rounded in silhouette and symmetrical in a two-dimensional axis. Furthermore, they have a complex internal anatomy consisting of bundled myelinated axons with investing Schwann cells surrounded by endoneurium. These collectively group to form fascicles, which in turn are surrounded by specialized perineural fibrocytes forming the perineurium. The perineurium is in turn associated collectively with other nerve fascicles and vessels surrounded by an epineurium (Fig. 24.6). Intravascular tumor extension is an uncommon histologic finding and when identified is most often seen in the context of high-grade neuroendocrine malignancies (i.e., Merkel cell carcinoma) or melanoma. In these instances, the malignant cells form cohesive clusters of principally hyperchromatic nuclei with scant amounts of cytoplasm that can be readily recognized in the context of the normal surrounding vascular anatomy. In the final analysis of difficult cases or if uncertainty should prevail, additional layers may yield a more readily identifiable vessel.

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Aggressive Spindle Cell Neoplasm

25

Rebecca S. Thornhill and Tyler Scott

A 79-year-old Caucasian male with a history of malignant spindle-cell neoplasm of the scalp not otherwise specified presented with a rapidly enlarging crateriform nodule. Based on the histologic features and location deep within the subcutaneous fat and fascial layers, the correct diagnosis is:

(a) Spindle squamous cell carcinoma
(b) Spindle-cell melanoma
(c) Pleomorphic undifferentiated sarcoma
(d) Leiomyosarcoma

The correct answer is (c), pleomorphic undifferentiated sarcoma. Low-power examination yielded a deeply seated spindle-cell neoplasm located in the subcutaneous fat and extending to the fascial plane (Fig. 25.1). At intermediate power, sweeping fascicles of spindled mononuclear and pleomorphic multinucleated cells are seen (Fig. 25.2), with increased numbers of typical and atypical mitotic figures (Fig. 25.3).

Pleomorphic undifferentiated sarcoma (PUS) not otherwise specified (NOS) as defined by the World Health Organization (WHO) in 2002 and previously known as malignant fibrous histiocytoma is the most prevalent soft-tissue sarcoma characteristically seen in older patients and is typically found within the deep soft tissue of the extremities or the retroperitoneum. Because no true cell of origin has been identified, many experts feel that PUS represents the final common pathway of different sarcomas that undergo dedifferentiation. PUS is defined by its deeper location within the subcutaneous fat or fascial plane. As such, it pursues a much more aggressive biologic course than its more superficially located counterpart, which is termed atypical fibroxanthoma (AFX). Histologically, the tumors may show overlapping characteristics of other sarcomas, presumably derived from other mesenchymal origins such as smooth muscle leiomyosarcoma,

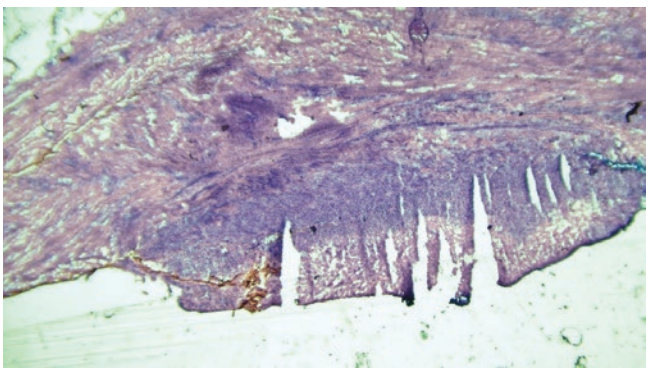

Fig. 25.1 Deeply seated spindle neoplasm. (*Courtesy of* PathologyOutlines.com. Undifferentiated pleomorphic sarcoma. http://www.pathologyoutlines.com/topic/softtissuemfhpleo.html; with permission)

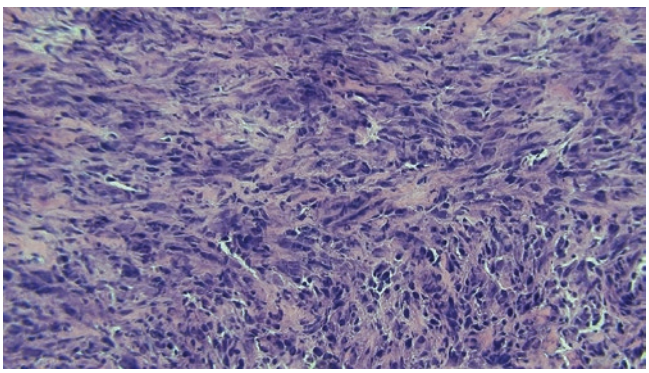

Fig. 25.2 Spindled mononuclear and pleomorphic multinucleated cells. (*Courtesy of* PathologyOutlines.com. From Undifferentiated pleomorphic sarcoma. http://www.pathologyoutlines.com/topic/softtissuemfhpleo.html; with permission)

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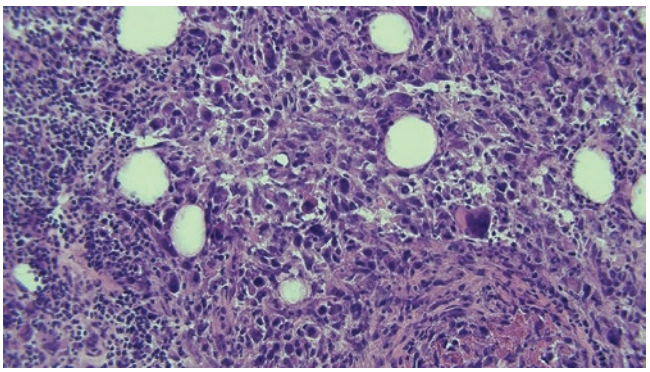

Fig. 25.3 Increased atypical mitotic figures. (*Courtesy of* PathologyOutlines.com. From Undifferentiated pleomorphic sarcoma. http://www.pathologyoutlines.com/topic/softtissuemfhpleo.html; with permission)

fibroblasts in fibrosarcoma, and skeletal muscle rhabdomyosarcoma. Thus it is considered a diagnosis of histologic and immunophenotypic exclusion. The differential diagnosis would additionally include a variety of epidermal and dermal tumors capable of spindle-cell or pleomorphic differentiation, including spindle-cell squamous cell carcinoma (SCC), spindle-cell melanoma, and leiomyosarcoma.

Spindle-cell SCC is considered to be a poorly differentiated form of squamous cell carcinoma and is most commonly encountered in sun-exposed skin areas of older patients, including the scalp. On gross examination, spindle-cell carcinoma can present as a smooth nodule, a fungating mass, or rarely as an ulcerated indurated plaque. Microscopically, the spindle cells grow as interlacing fascicles or in storiform arrangements. Important histologic clues include a connection with or approximation with the overlying epithelium, keratinizing foci including dyskeratosis appreciated as densely eosinophilic cytoplasm, and a predilection for perineural extension. Immunohistochemical stains for cytokeratin can differentiate spindle-cell carcinoma from sarcomas and melanomas.

Spindle-cell melanoma is a less common histologic variant of vertical growth phase melanoma that like SCC is seen principally in sun-exposed areas of older patients. The typical features of epithelioid melanoma are not seen in spindle-cell melanoma. Thus it is imperative to differentiate this neoplasm from a sarcoma. Important histologic clues include an intimate association with the overlying epithelium, a significant degree of cellular cohesion, associated epithelial and pagetoid cells within the epithelium, intracytoplasmic and extracellular melanin pigment, and inconspicuous nucleoli [1]. S-100 remains the most reliable immunohistochemical marker for demonstrating spindle-cell melanoma cells, with Sox-10 being an additional important marker. Melan-A/Mart-1 and HMB-45 are less reliable markers for spindle-cell or desmoplastic melanoma.

Leiomyosarcoma presents in two guises, either cutaneous tumors that derive from the arrector pili muscles of hair follicles within the dermis or subcutaneous tumors that originate from the tunica media of an artery or vein of deeper anatomic strata such as the subcutaneous fat or fascial plane. The cutaneous tumors follow a more benign course, whereas the subcutaneous location is axiomatic of all malignant spindle-cell mesenchymal tumors, which pursue a much more aggressive course. The overwhelming majority of non-visceral soft-tissue leiomyosarcomas are located on the extremities and are of the subcutaneous type [2]. Among the entities discussed, a leiomyosarcoma may also arise within the viscera and metastasize or extend into the skin. Valuable histologic features of leiomyosarcomas include a predisposition to form sweeping fascicles that intersect at right angles with cells containing cigar-shaped nuclei, characteristic perinuclear vacuoles at one or both ends of nuclei, and intracytoplasmic striations imparting a slightly granular appearance. Smooth muscle actin is the most sensitive immunohistochemical stain for leiomyosarcoma. However, since a minority of PUS and AFXs may stain with actin, desmin remains the most specific and ideal marker in the differentiation of leiomyosarcoma from AFX/PUS.

The most important entity to be distinguished from pleomorphic undifferentiated sarcoma is its dermal analog known as atypical AFX. AFX is typically found on the head and neck of individuals in the seventh decade and is related to ultraviolet exposure. AFX and pleomorphic undifferentiated sarcoma possess a dual fibroblastic and mononuclear histiocytic lineage. Therefore, they have overlapping ultrastructural, histochemical, and histologic attributes. The distinction between the two lies principally in their location and in their ability to extend into deeper strata [3]. Microscopically, AFX presents as a well-circumscribed dermal tumor, extending only to the superficial subcutis, with spindled and irregular cells in haphazard arrangements and atypical mitotic figures [3]. Tumor necrosis is rarely observed. Immunohistochemical analysis yields similar results in AFX and PUS. Both are characteristically positive for CD-68, vimentin, and CD-10. Only CD-74 (strongly positive in PUS, weakly positive in AFX) and CD-99 (negative in PUS and positive in 35–75% of AFX cases) show contrasting results [4].

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Eyelid Tumor

26

Nicole Asher and Tyler Scott

A 55-year-old woman presented with a rapidly growing 1.5-cm ulcerated lesion on the right lower eyelid. Low-power microscopic section yielded a picture of a vaguely nodular dermal proliferation of lightly eosinophilic and vacuolated cells (Fig. 26.1). At intermediate power, the neoplastic nodules consisted of a random admixture of optically clear and eosinophilic stained cells (Fig. 26.2). High-power examination yielded vacuolated cells composed of hyperchromatic nuclei (Fig. 26.3).

The correct diagnosis is:

(a) Sebaceous carcinoma
(b) Basal cell carcinoma with clear cells
(c) Squamous cell carcinoma
(d) Sebaceous adenoma

The correct answer is (a), sebaceous carcinoma. The differential diagnosis includes sebaceous adenoma, basal cell carcinoma (BCC) with clear cells, and squamous cell carcinoma (SCC).

Sebaceous carcinomas are separated into two categories based on their pattern of behavior, either periocular or extraocular. These tumors can arise de novo or as sequelae of Muir–Torre syndrome (MTS), which itself is associated with hereditary nonpolyposis colorectal cancer syndrome (HNCCS). MTS is associated with an increased risk of visceral malignancy; therefore, it is recommended that all patients with sebaceous carcinoma be screened for the lack of expression of DNA mismatch repair genes (MMRs) or microsatellite instability [1]. Malignant sebaceous tumors are more likely to occur in the periocular region (as opposed to adenomas or sebaceomas) and are less often associated with MTS compared with their extraocular counterparts. Those located in the periocular region can arise from the meibomian glands, the glands of Zeis, or the sebaceous glands of the eyelid. These tumors comprise approximately three quarters of all sebaceous carcinomas and are the second or third most common eyelid malignancies after BCCs and SCCs.

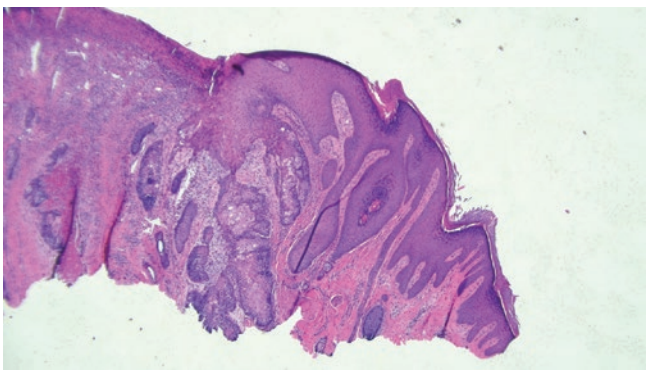

Fig. 26.1 Nodular dermal proliferation of eosinophilic and vacuolated cells

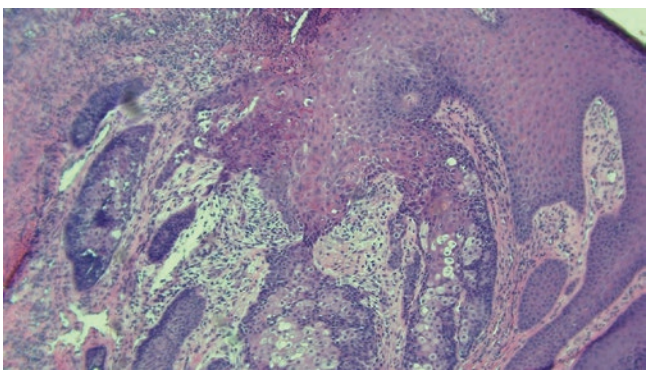

Fig. 26.2 Optically clear and eosinophilic stained cells

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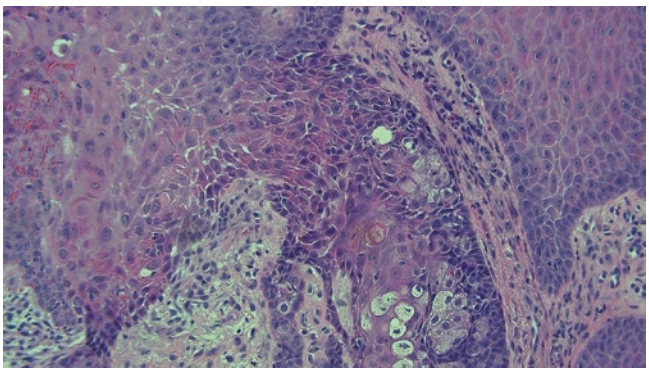

Fig. 26.3 Vacuolated cells with hyperchromatic nuclei

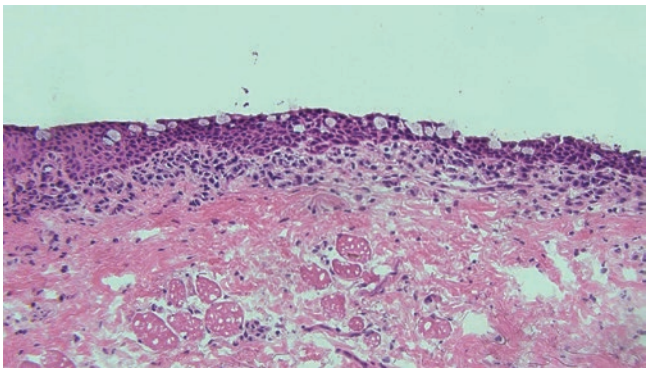

Fig. 26.4 Mucus-filled goblet cells of the conjunctivae

On gross examination, sebaceous carcinoma presents as a painless, firm, subcutaneous nodule most commonly located on the upper eyelid. These lesions may resemble inflammatory lesions such as a chalazion or blepharoconjunctivitis [2]. The histologic evaluation of sebaceous lesions poses a considerable diagnostic challenge. Histologically, periocular sebaceous carcinomas often exhibit an infiltrative architectural pattern within the dermis that extends into the superficial muscle and subcutaneous tissue of the eyelid. The tumor cells are enlarged, with pleomorphic amphiphilic cells with hyperchromatic nuclei and frequent mitotic figures. Depending on the degree of differentiation, sebaceous carcinomas may show obvious or only focally mature sebocytes consisting of intracytoplasmic vacuolization. A characteristic feature of periocular sebaceous carcinoma is intraepithelial or pagetoid spread involving the bulbar and palpebral conjunctiva and the cornea [3]. Epithelial involvement is rarely encountered in extraocular cases. The clinician should have a high degree of suspicion with regard to sebaceous differentiation in the periocular region, since benign sebaceous neoplasms are not common in this region. Clinical challenges notwithstanding, additional difficulties encountered by the microscopist in the periocular adnexa include the conjunctivae, which normally contain mucus-filled goblet cells that may simulate sebaceous carcinoma (Fig. 26.4).

In regard to the histologic differential diagnosis, sebaceous adenoma can be distinguished by a horizontal as opposed to a vertical orientation in the dermis, symmetric interlobular and intralobular homology, and the orderly maturation of and prevailing percentage of mature lipid-laden central sebocytic cells over peripheral lobular germinative basaloid cells. Cytologically, the absence of mitotic figures and hyperchromatic nuclei favors a diagnosis of sebaceous adenoma. The two most common malignant tumors identified in the periocular region are BCC and SCC. BCC with clear differentiation is distinguished from sebaceous carcinoma by virtue of the presence of peripheral palisading, lack of pagetoid intraepithelial spread, tumor stromal cleft artifacts (not a reliable feature in frozen section), and mucinous spindle-cell stroma. Additionally, BCC is associated with early-stage ulceration, a finding not consistent with sebaceous carcinoma. The difference in the appearance of SCC lies in the type of cytoplasmic content. Sebaceous gland carcinoma contains amphophilic-to-clear, often vacuolated cytoplasmic contents, whereas SCC is eosinophilic in squamous-cell carcinoma. SCC is often accompanied by disparate cells representing faulty keratinization and appearing as densely eosinophilic cells with pyknotic nuclei as well as squamous eddies and overlying epithelial parakeratosis. Immunostaining can differentiate sebaceous carcinoma from BCC and SCC. Sebaceous carcinomas are consistently epithelial membrane antigen (EMA)-positive, adipose differentiation-related protein (ADP)-positive, and androgen receptor (AR)-positive. Squamous cell carcinoma is EMA-positive, AR-negative, and ADP, whereas basal cell carcinoma is EMA-positive and ADP [4].

The differential diagnosis of intracytoplasmic vacuoles (optically clear epithelial cells) is (1) intracytoplasmic storage lipid, as encountered in sebocytes or xanthoma cells; (2) glycogen or glycosaminoglycans, as encountered in the conjunctival goblet cells or eccrine duct cells; and (3) water (hydropic degeneration), which is typically seen in the epithelial mucosal sites of chronic irritation or allergic contact dermatitis. Historically, special stains for lipids (e.g., Oil Red O) on fresh frozen tissue have assisted in further confirmation of the diagnosis. Recently, adipophilin, a monoclonal antibody that binds to the surface of intracellular lipid droplets, has gained interest as a means of differentiating clear cell on histologic examination. Adipophilin is expressed in sebaceous and xanthomatous lesions but not in SCC, BCC, or any other clear cell lesions [5].

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Non-melanoma Skin Cancer with Anemia

27

Rebecca S. Thornhill and Tyler Scott

A 75-year-old man with a history of multiple cutaneous squamous cell carcinomas (SCCs) and chronic lymphocytic leukemia (CLL) presented with a rapidly growing nonscaly nodule adjacent to a site of previous Mohs surgery. Microscopic examination yielded these findings. The correct diagnosis is:

(a) Rosacea
(b) Perineural lymphocytic infiltrates associated with a previous history of SCC
(c) Cutaneous lupus erythematosus
(d) Small lymphocytic lymphoma/chronic lymphocytic leukemia associated with site of previous surgery and scarring

The correct answer is (d), small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (SLL/CLL) associated with site of previous surgery and scarring. Microscopic sections at low power (Fig. 27.1) show an essentially normal epithelium and dermis with increased vellus follicles, sebaceous hypertrophy, and solar elastosis typical of the anatomic location and patient's age and gender. The deeper dermis discloses a dense diffuse and nodular lymphoid infiltrate. Scrutiny of the lymphoid infiltrates (Fig. 27.2) shows irregular round, elongated, and infiltrating strands of uniform-appearing lymphocytes and smaller foci of interspersed larger epithelioid-appearing cells (Figs. 27.3, 27.4). The differential diagnosis includes perineural lymphocytic infiltrates associated with a previous history of SCC, cutaneous lupus erythematosus, rosacea, cutaneous lymphoid hyperplasia, or changes consistent with the previous medical history of CLL (Fig. 27.4).

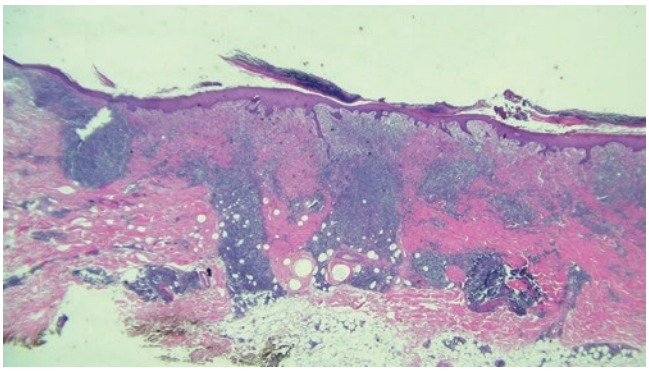

Fig. 27.1 Normal epithelium with increased vellus follicles, sebaceous hypertrophy, and solar elastosis

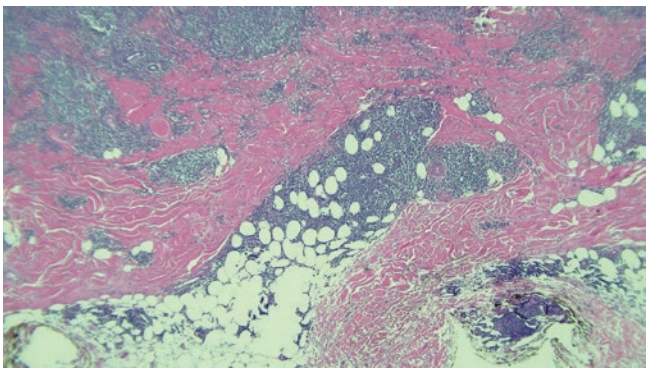

Fig. 27.2 Infiltrating strands of uniform-appearing lymphocytes

Small lymphocytic lymphoma and chronic lymphocytic leukemia are hematopoietic malignancies involving an identical cell lineage, the former representing fixed tissue sites [1]. The most common fixed tissue or static organs involved include the reticuloendothelial system of the liver, spleen, bone marrow, and lymph nodes, although all organs including the skin may be involved. While these overlapping enti-

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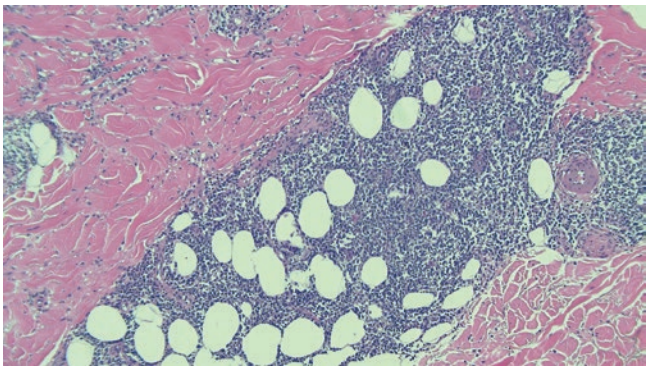

Fig. 27.3 Smaller foci of larger epithelioid-appearing cells

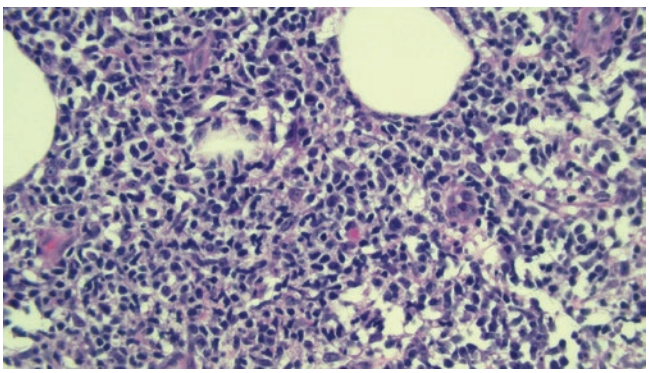

Fig. 27.4 Lymphocytes with plasmacytoidic dendrocytes

ties are considered to be a low-grade lymphoproliferative disorder that most commonly afflicts the elderly, long-term complications, including anemia and neutropenia, inevitably ensue, with infection being the most likely ultimate cause of demise in these patients. In most instances the skin is secondarily involved by the circulating form of the disease and is only rarely the site of de novo fixed disease or presentation. Because the typical patient with SLL/CLL is older and this entity is associated with waning immunity, these patients are relatively immunocompromised. Therefore they have or continue to develop non-melanoma skin cancer and particularly squamous cell cancer in sun-exposed areas; this occurrence has been reported to be nine times more likely in these patients [2]. These cutaneous malignancies may be obscured by the neoplastic elements both within the tumor foci and in more advanced cases involving perineural locales. The lymphocytic infiltrates may not only obscure delineation of the tumor but also may pose considerable diagnostic difficulty when perineural invasion is considered. The neoplastic elements in SLL/CLL are typically of B lymphocytic lineage and possess a distinctive and anomalous cell surface CD antigen repertoire of CD-5 and CD-20 coexpression along with CD-23 expression [3]. The atypical lymphocytes form nodular and/or irregular aggregates that can be seen occupying all levels of the dermis and subcutaneous fat. They are characterized by a monomorphic or uniform cytologic appearance with increased numbers of mitotic figures or apoptotic cells. Interspersed clear zones with proliferation centers are typical of these infiltrates and are a useful feature in distinguishing these infiltrates from reactive simulants.

The differential diagnosis in this setting includes rosacea, lupus erythematosus, and cutaneous lymphoid hyperplasia or benign lymphocytoma cutis. The infiltrates of rosacea such as SLL/CLL are predominately lymphocytic. However, admixed histiocytes, plasma cells, and neutrophils are frequently identified. The infiltrates of rosacea are typically seen in a perifollicular distribution and are accompanied by capillary ectasia seen within the vasculature of perivascular locales. Lupus erythematosus similar to the rosacea shows a predominance of lymphocytes. However, increased numbers of plasma cells and specialized plasmacytoid cells called plasmacytic dendrocytes are seen [4]. These cells are situated around follicles as well as the eccrine ducts. Other histopathologic features of lupus erythematosus include an alignment of lymphocytes along the dermal/epidermal junction and other changes accompanying interface dermatitis. These changes include dyskeratotic epithelial cells, a thickened basement membrane, and melanin incontinence. Cutaneous lymphoid hyperplasia or lymphocytoma cutis is the most difficult entity to distinguish from the foregoing entities, but important clinical and pathologic attributes usually allow for its distinction. The typical clinical setting is of a solitary persistent erythematous nodule with a predilection for development on the scalp or face. The pathology shows nodular and diffuse collections of lymphocytes with the formation of germinal centers/lymphoid follicles. The lymphoid follicles consist of round to oval aggregates of larger clear cells surrounded by a cuff of smaller, denser staining lymphocytes forming a mantle around the germinal center areas. The infiltrates on higher power examination show a polymorphic composition of lymphocytes and other types of cells, including plasma cells. The lymphocytes themselves are of a dissimilar appearance with different shapes and sizes. Small clear zones or proliferation centers typical of SLL/CLL are not seen.

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Follicular Neoplasm

28

Tyler Scott and Nicole Asher

A 60-year-old Caucasian man with biopsy-proven basal cell carcinoma (BCC) underwent Mohs surgery. Second-stage microscopic examination yielded this finding. The diagnosis is:

(a) Basaloid follicular hamartoma
(b) Trichoblastoma
(c) BCC with follicular extension
(d) Tangentially cut follicular structure

The correct answer is (c), basal cell carcinoma with follicular extension. Microscopic sections yielded low-power findings of a distorted follicle with sebaceous glands to the left and scars to the right (Fig. 28.1). Intermediate power showed a basaloid tumor circumscribing the upper (infundibular) portion of the follicle and extending asymmetrically into the adjacent epithelium (Fig. 28.2). Higher power revealed a subtle pale myxoid matrix circumscribing the periphery of the BCC (Fig. 28.3).

The follicle is a complex multifunctional apparatus composed of the basilar germinative portion of the hair shaft that gives rise to the pilomatricoma, the middle isthmic portion bounded by the arrector pili muscle inferiorly and the sebaceous duct superiorly, the source of tricholemmoma, and finally the keratinized upper portion termed the infundibulum [1].

Follicular BCC must be distinguished from similar appearing neoplasms of hair matrix differentiation. These tumors are often seen in patients with germline mutations predisposing them to adnexal tumors.

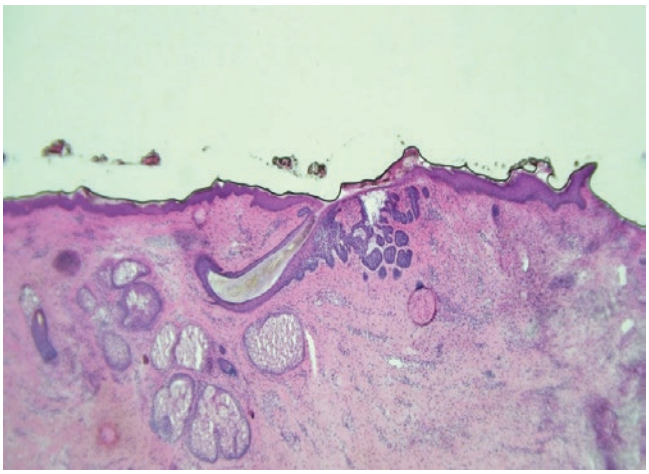

Fig. 28.1 Distorted follicle with basaloid tumor

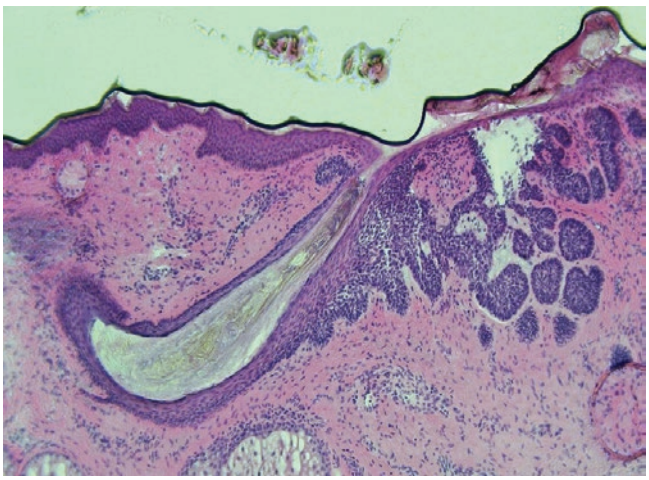

Fig. 28.2 Basaloid tumor involving follicle and adjacent epithelium

The most important benign simulants of BCC, known collectively as trichoblastoma or trichoepithelioma, principally derive from the isthmus and basilar portions of the follicle. As

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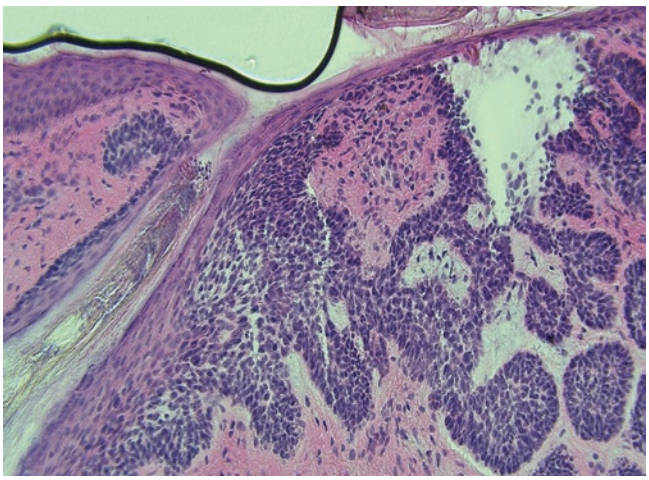

Fig. 28.3 Basaloid tumor with surrounding myxoid matrix

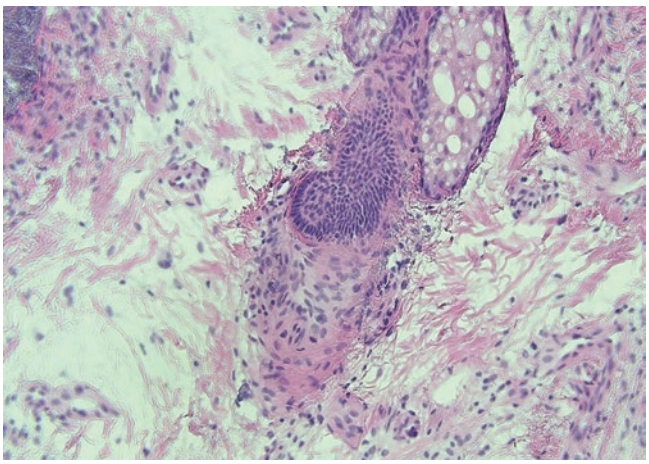

Fig. 28.4 Basaloid focus with internal complexity and eosinophilic membrane

such, variable differentiation toward the lumen (ductular), the outer root sheath, the inner root sheath, and the base (follicular germs) may be seen [1]. Microscopically, these neoplasms appear as aggregated basaloid keratinocytes surrounded by fibroblasts and mesenchymal cells with a growth pattern that resembles an embryologic hair follicle. Other entities that have been found to display follicular differentiation are pilomatricoma, basaloid follicular hamartoma, and pilar sheath acanthoma.

Pilomatricomas are rare neoplasms, but they are associated with a high rate of local reoccurrence. They consist of a highly proliferative basaloid component with hair-like abrupt keratinization and ghost cells. Occasionally, BCC will display matrical differentiation with anucleated shadow cells adjacent to the islands of proliferating basaloid cells mimicking pilomatricoma [2].

Another differential diagnostic possibility is a basaloid follicular hamartoma. These benign tumors are visualized microscopically as cords and strands displaying a branching growth pattern resembling that of infundibulocystic BCC. A full-thickness skin biopsy is required to differentiate basaloid follicular hamartoma from BCC and trichoepithelioma. Of note, these neoplasms are linked to mutations in the PTCH gene, the same mutation that is thought to be the cause of the nevoid BCC syndrome [3]. The question has been asked as to whether this lesion is a precursor of BCC. Close monitoring may be required at follow-up examination.

Among the most difficult challenges to the microscopist of Mohs surgery is to distinguish tangentially cut (telescoped) follicles, particularly vellus follicles of the face that show duplicated mantle projections or angulated follicular germs simulating BCC with follicular extension. Like BCC, these rudimentary structures are basaloid in appearance and show an intimate connection with the follicle (Fig. 28.4). However, reliable histologic criteria can be applied to distinguish them, including (1) a differentiated internal composition that often includes centrally located zones made up of cells that assume a different orientation compared with cells of the peripheral layer; (2) a thin eosinophilic basement membrane lacking in BCCs; (3) the absence of a surrounding myxoid matrix typical of BCCs; and (4) extension of basaloid foci to the adjacent epithelium with BCC.

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Hemorrhagic Papule in a Patient with Lip Carcinoma

29

Rebecca S. Thornhill and Tyler Scott

An 84-year-old male with a history of basal cell carcinoma (BCC) of the scalp presented with an ulcerating nodule. Low-power microscopic sections yielded an irregular surface epithelial and dermal basaloid neoplasm (Fig. 29.1). Intermediate-power examination showed extensive follicular involvement at all levels of the follicle (Fig. 29.2). High-power examination revealed a two-toned basophilic peripheral layer with central eosinophilic staining (Fig. 29.3).

The correct diagnosis is:

(a) Keratinizing BCC
(b) Poorly differentiated squamous cell carcinoma (originally misdiagnosed)
(c) Basosquamous carcinoma
(d) Sebaceous carcinoma

The correct answer is (b), poorly differentiated squamous cell carcinoma. Squamous cell carcinoma (SCC) is the second most common skin cancer following BCC. Similar to BCC, it is more prevalent in areas with excessive exposure to ultraviolet radiation and is associated with advancing age and cumulative sun exposure [1]. While both tumors may be locally invasive, SCC has a greater metastatic potential and thus carries a higher risk of progressive disease. Histologically, SCC can be broadly subdivided into three grades based on the degree of nuclear atypia and keratinization (well, moderate, and poor) with increasing dedifferentiation representative of a worse prognosis [1]. The majority tend to be well differentiated with slightly enlarged and hyperchromatic nuclei with abundant cytoplasm and produce large amounts of keratin, giving the characteristic appearance of keratin pearls [2]. On the other hand, poorly differentiated tumors demonstrate markedly enlarged and pleomorphic nuclei that have a high nuclear to cytoplasmic ratio and demonstrate a high degree of atypia and frequent mitoses [2]. Keratin production in these variants is diminished. Moderately differentiated tumors share characteristics of both variants. Since various subtypes of SCC demonstrate different clinical behaviors, distinguishing among these variants microscopically is important with regard to treatment and overall outcomes [1].

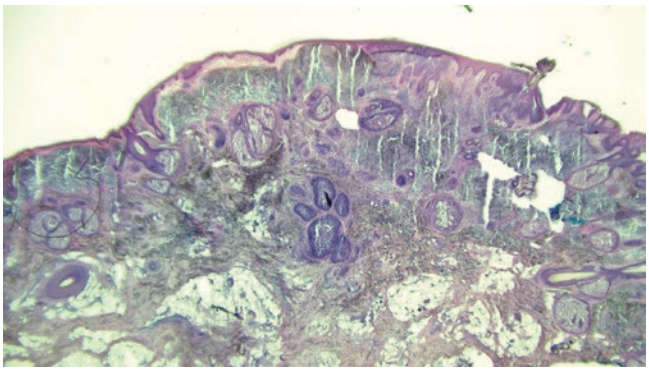

Fig. 29.1 Basaloid neoplasm on epithelial surface and within dermis

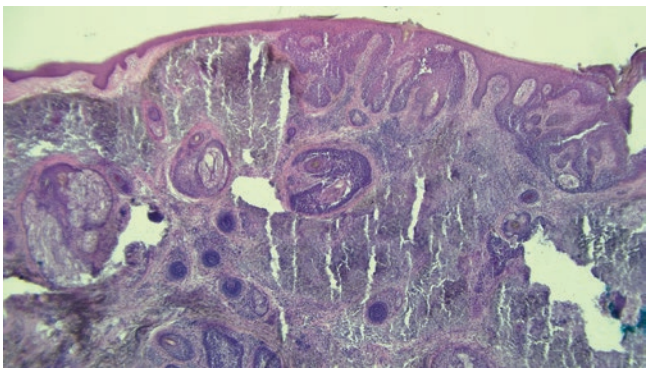

Fig. 29.2 Neoplasm occupies all levels of the follicle

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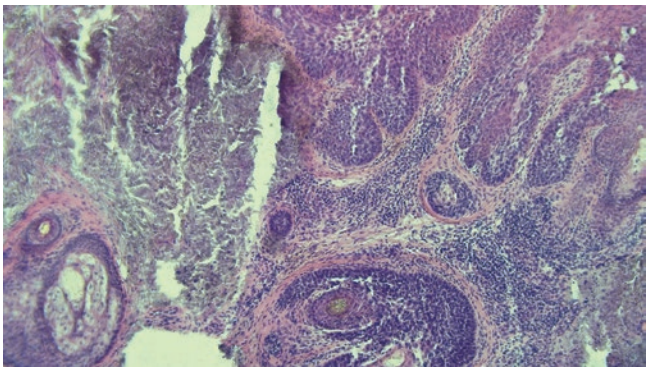

Fig. 29.3 Two-toned basaloid and centrally eosinophilic neoplasm

Poorly differentiated SCCs should be distinguished from keratinizing BCC, basosquamous carcinoma, and last sebaceous carcinoma. Key histologic attributes of SCC, including poorly differentiated examples, include (1) foci of eosinophilic keratinization (usually central as seen in Fig. 9.3) and/or dyskeratosis; (2) a propensity for extension through all layers of the follicle (including the isthmus and the bulb as seen in Fig. 9.2) and/or for extension through acrosyringia; and (3) the absence of myxoid peritumoral stroma as seen in keratinizing BCC or sebocytic differentiation as seen in sebaceous carcinoma.

Microscopically, BCC characteristically exhibits proliferation of basaloid cells with scant cytoplasm, hyperchromatic nuclei, peripheral palisading, and peritumoral myxoid stroma [2]. Particular microscopic difficulty may be posed by the keratinizing form of BCC in cases revealing tumor cells that appear squamoid or exhibit ample eosinophilic cytoplasm mimicking the appearance of SCC [1]. The keratinizing foci, however, should lack atypical cytologic features consisting of hyperchromasia, nuclear irregularity, notching, or the presence of mitoses. These atypical cytologic features would qualify the neoplasm as a basosquamous carcinoma [3]. In such ambiguous cases, immunochemistry may prove a useful diagnostic tool in that BCC is positive for Ber-EP4 and bcl-2 while SCC is uniformly negative for these markers [1].

Considered an aggressive subtype of BCC, basosquamous carcinoma, also referred to as "metatypical BCC," is a biphasic tumor composed of malignant peripheral palisading basaloid and central malignant squamous epithelium [4]. Microscopically, these tumors may present with a transition zone between BCCs and SCCs [4], although this is not required for the diagnosis. Like BCCs, they may exhibit peripheral palisading mitoses and stromal collagen; however, the basaloid cells are more mitotically active with greater numbers of apoptotic nuclei [4].

An uncommon but aggressive skin cancer that also carries a predilection for the head and neck is sebaceous carcinoma, also referred to on the eyelid as meibomian gland carcinoma [5]. The meibomian glands are modified sebaceous glands without the interposed follicles that are found in association with the upper and lower tarsal eyelid plates [5]. Microscopically, tumor cells show distinct features of cells with sebocytic differentiation with characteristic enlarged nuclei, prominent nucleoli, and most important, lipid cytoplasmic vacuoles. Sebaceous carcinomas may present in the histologic guise of SCCs when they exhibit only focal sebocytic differentiation [5]. In these rare cases immunohistochemical staining with epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), or cytokeratin 7 (CK7) will elucidate the correct diagnosis [5].

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Blue Ball in the Dermis

30

Rebecca S. Thornhill and Nicole Asher

A 77-year-old man with a history of nodular basal cell carcinoma excised from the scalp 5 years prior presented with complaints of scalp tenderness for the past three weeks. Examination yielded a well-healed scar with surface scale. The initial stage showed a parakeratotic epithelium (Fig. 30.1) subtended by a deep dermal scar and a basophilic-staining subcutaneous nodule (Fig. 30.2). The nodule is vaguely rounded and partially surrounded by an eosinophilic capsule (Fig. 30.3). The cells are densely chromatic, lack palisading, and are admixed with vacuolated cells (Fig. 30.4). The correct diagnosis is:

(a) Lymph node
(b) Basal cell carcinoma
(c) Benign follicular hamartoma
(d) Trichoepithelioma

The correct answer is (a), lymph node. The recognition of lymph nodes and lymphoid infiltrates in fresh frozen biopsy material is extremely problematic, particularly in the foregoing clinical setting with concern for basal cell recurrence. However, lymphoid infiltrates and nodal collections have reproducible histologic features that can be readily relied upon in their distinction from basal cell carcinoma and from adnexal neoplasms that may pose diagnostic problems. Benign (reactive) lymphoid aggregates are typically encountered in the context of rosacea on head and neck locations cohabitated by nonmelanoma skin cancer [1]. These infiltrates are predominantly made up of lymphocytes but will show appreciable numbers of both plasma cells and neutrophils. The preferential location of the aggregates for adnexal structures, particularly the hair follicle, is key to their recognition. Accompanying features of lesser diagnostic importance include perifollicular epithelioid granulomata and vascular ectasia; the latter feature responsible for the clinical erythema, while sensitive to the diagnosis, is not specific to the diagnosis since it is often present in the dermatoheliotic skin specimen. Rarely, lymphoid infiltrates may be seen either along the dermoepidermal junction in the context of a lichenoid dermatosis or near the eccrine ducts

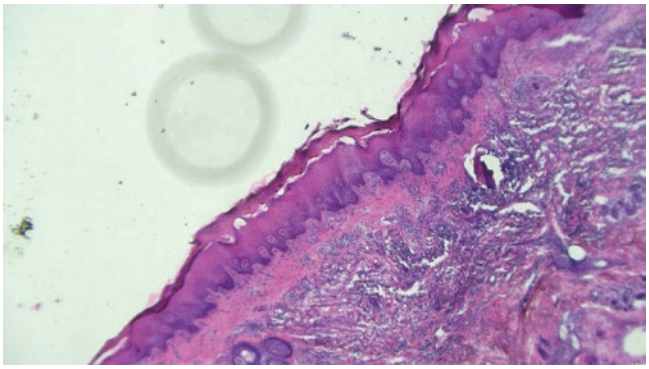

Fig. 30.1 Parakeratotic epithelium

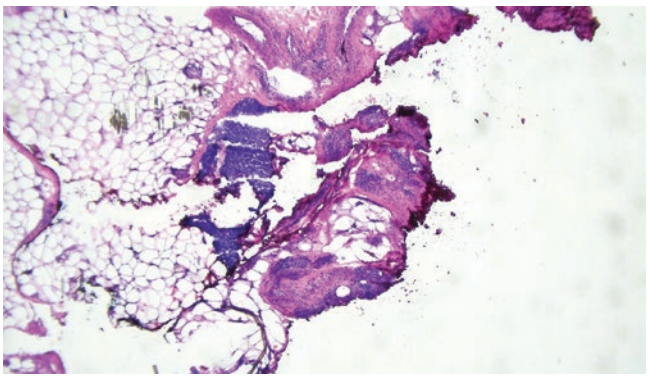

Fig. 30.2 Deep dermal scar and basophilic-staining subcutaneous nodule

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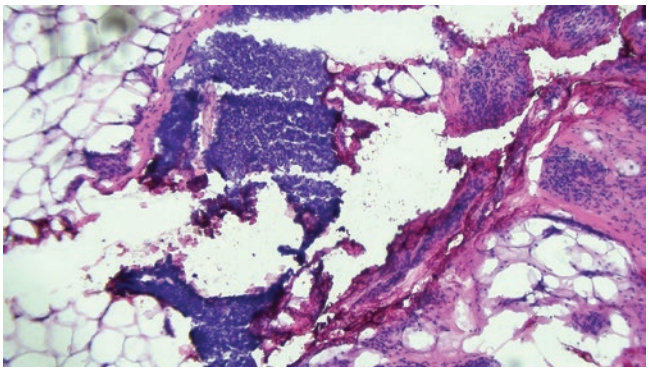

Fig. 30.3 Rounded nodule surrounded by eosinophilic capsule

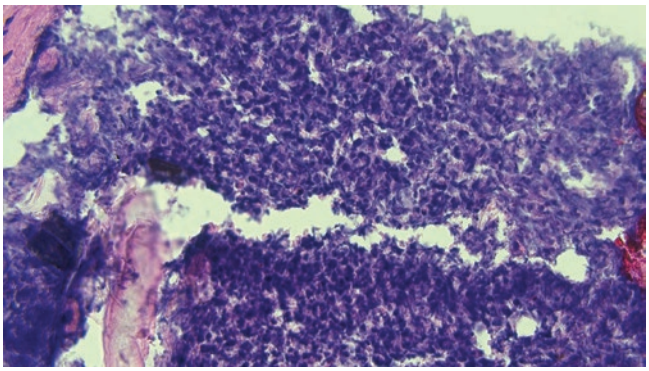

Fig. 30.4 Densely chromatic cells admixed with vacuolated cells

and glands in cutaneous lupus erythematosus [2]. It is important to remember that hypertrophic and ulcerative lesions of lichen planus as well as chronic discoid lesions of cutaneous lupus erythematosus predispose to squamous cell carcinoma. Reactive lymph nodes are rarely encountered within the skin, and when present they are typically found in the subcutaneous fat layer [3]. The most common context that the Mohs surgeon would discover in their presence is the setting of a remotely healed surgical site similar to the above example. Successful discrimination relies upon the clinical context and particularly on histologic features. These features include key low-, intermediate-, and high-power microscopic features [4]. At low power, it is important to remember that lymph nodes are most often found within the subcutaneous fat and possess a round-to-oval symmetric orientation. At intermediate power, the lymph node is surrounded by a retractile eosinophilic band of fibrous tissue referred to as the capsule. At high power, the cellular constituency is principally dense chromatic and uniform in size. Typically, scattered clearer larger cells (antigen-presenting cells) can be found. Larger (>0.5 cm) lymph nodes show light and dark zonation throughout, with the darker areas corresponding to the follicles and the clearer zones to the interfollicular and subcapsular areas of the lymph node sinus.

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