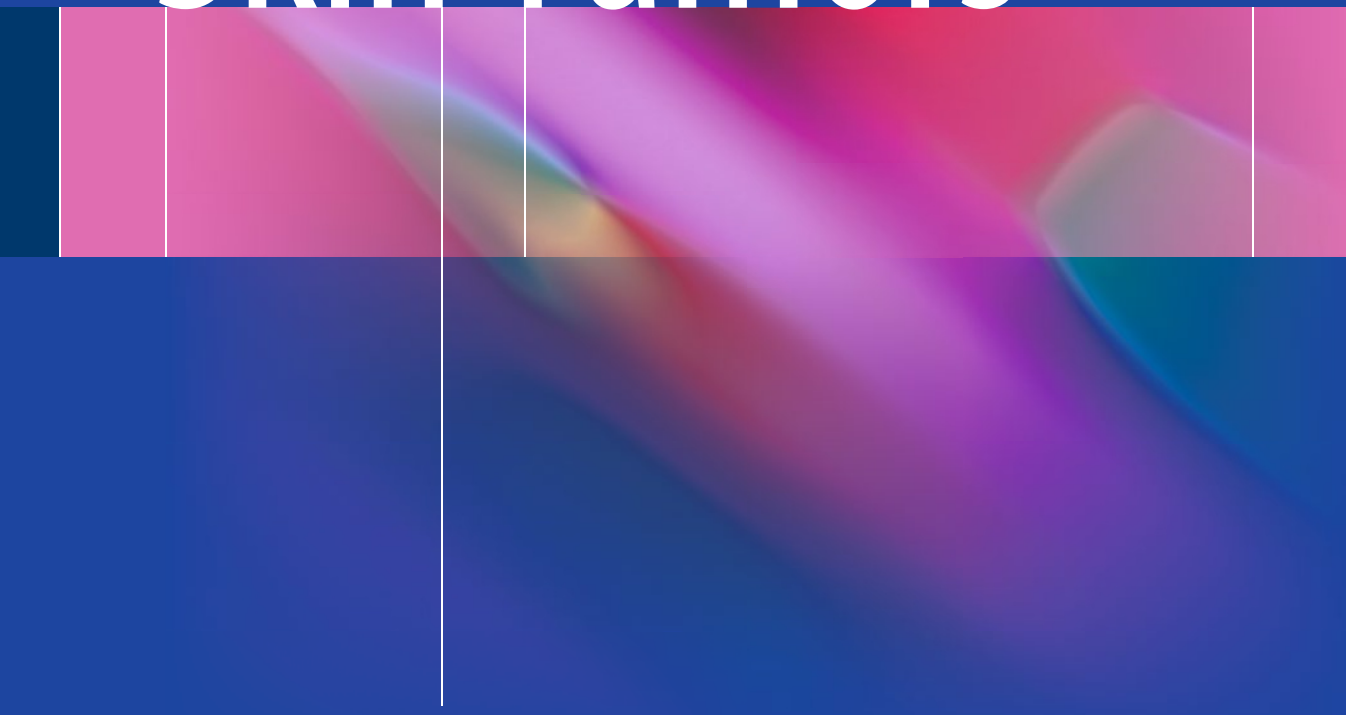
Franco Rongioletti · Irina Margaritescu
Bruce R. Smoller

Rare Malignant Skin Tumors



Springer

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Franco Rongioletti
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Editors

Rare Malignant Skin Tumors

With the contributions of Werner Kempf

Springer

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Foreword

Fostered by immunohistochemical and molecular techniques, over the past decade there have been tremendous advancements in the fields of pathology in general and of dermatopathology in particular. Against a background of specific and highly advanced therapeutic modalities, including targeted therapy, the precise histopathological diagnosis of malignant tumors is paramount for the patient's prognosis, well-being, and the general quality of life.

Dermatopathologists are aware of a growing number of very important, albeit quite rare, malignant cutaneous tumors which deserve special diagnostic attention. These tumors must be feared for three main reasons: (1) most of them are exceedingly rare and may be once-in-a-lifetime encounters for many pathologists, resulting in a high yield of misdiagnoses; (2) many of these tumors like to camouflage behind a seemingly innocent inflammatory or tumor pattern, e.g. pseudolymphomatous angiosarcoma imitating cell-rich rosacea or digital papillary adenocarcinoma looking like a benign cystic hidradenoma, which makes them the proverbial wolves in sheeps' skin; and (3) these tumors often exhibit striking morphological overlap with other malignant tumor entities, e.g. epithelioid sarcoma versus pseudomyogenic hemangioendothelioma, or with cutaneous conditions generally considered to be entirely benign, e.g. epithelioid sarcoma versus granuloma annulare. For pathologists it is paramount to be constantly aware of this diagnostic mine field as most of the difficulties and consequential mistakes encountered in the daily sign-out of tumor cases are situated right here.

A most welcome and highly competent help to overcome this *diagnostic gap* is presented in *Rare Malignant Skin Tumors*. Franco Rongioletti, Irina Margaritescu and Bruce Smoller together with 12 co-workers have amassed an exquisite collection of 70 cutaneous tumor entities which represent the crème de la crème of rare cutaneous malignancies which one should never diagnostically miss. These malignancies represent the *must-know canon* of advanced cutaneous tumor pathology. The present tome has a wonderful dual quality as it can be used in two ways, both as a textbook and as a check-list or manual next to the microscope. The textbook quality is obvious: entities are presented in a quite clear and concise way, in conjunction with excellent photomicrographs. Relevant points of interest, in particular pitfalls and differential diagnoses, are pointed out. The latest immunohistochemical and molecular

findings are included. The text is well-referenced. Foremost, all chapters are written by experts in the field, a quality which shines through each paragraph and is highly appreciated by the practicing pathologist. Reading this book from cover to cover should be an absolute must! Conversely, the text format chosen by the authors is ideally suited for a place next to the microscope: a crisp manual like this one is desperately needed in controversial cases as it renders invaluable services by pointing out the relevant points to follow and pitfalls to circumnavigate.

With remarkable love for morphology and didactic talent, Franco Rongioletti, Irina Margaritescu and Bruce Smoller produced a stupendous book that without question is filling a significant gap in the dermatopathologic literature. Without question, for the practicing pathologist and dermatopathologist *Rare Malignant Skin Tumors* will be an everlasting friend.

Friedrichshafen, Germany Heinz Kutzner

Foreword

I was delighted to learn that my good friends and colleagues, Franco Rongioletti and Bruce Smoller, together with the talented Irina Margaritescu, have again undertaken a book focused on an area of dermatopathology that, as it were, needs to be placed "under the microscope"! In this case, the subject is Rare Malignant Skin Tumours.

In the current era, when biopsies are more frequent, international communications more common, and diagnostic tools available to the pathologist ever more sophisticated, the recognition of unique manifestations and patterns of disease inevitably leads to the discovery and categorization of "new" clinicopathologic entities. The resulting generation of a bewildering array of disorders creates particular challenges for the practitioner, especially the individual whose chosen fields are dermatology and pathology. The availability of a concise but thorough, well-written and well-illustrated guide to such diseases is therefore of immense value.

And that is certainly the case for this volume on Rare Malignant Skin Tumours. The Table of Contents makes clear the scope of the book, which includes the entire spectrum of cutaneous tumors but focuses on those that are less common; that is, tumors that typically form a minority of one's practice but (1) are established entities, (2) often come up in the differential diagnosis of more common tumors, and (3) are important to recognize because of significant prognostic and treatment implications. Thus, for example, extramammary Paget's disease is a well-known condition that perhaps appears only now and then in a routine private practice. Yet, it is frequently an important consideration in the differential diagnosis of other more common disorders, such as pagetoid Bowen's disease, pagetoid dyskeratosis, or epidermotropic T-cell lesions. Its potential association with adnexal carcinoma and other malignancies (20–30 % of cases) places particular demands upon diagnostic accuracy in order to insure appropriate management. Primary mucinous carcinoma of the skin must be distinguished from metastatic mucinous adenocarcinoma, a process that requires the recognition of subtle histopathologic clues, such as the presence or absence of an in situ component surrounded by myoepithelial cells. Despite its rarity, pseudomyogenic hemangioendothelioma should be considered in the differential diagnosis of epithelioid sarcoma. Both occur on the distal extremities of young men, and in both cases the

neoplastic cells are cytokeratin positive, yet the epithelioid cells in pseudomyogenic hemangioendothelioma are distinctive by expressing an array of endothelial markers. The distinction is critical, considering the indolent biologic course of pseudomyogenic hemangioendothelioma when compared to that of epithelioid sarcoma.

The details that help one to accomplish these important diagnostic tasks are carefully described in this book, and include subtle morphologic clues, immunohistochemical findings, and molecular diagnostics. Microscopic images are of course essential for this purpose, and the ones in this volume are of particularly high quality.

In summary, this is an outstanding work on a much-needed topic. I strongly recommend that you purchase a copy and keep it near your microscope, where no doubt it will rapidly become dog-eared from frequent use! As always, I wish the authors every success with this impressive effort.

Charlottesville, VA, USA James W. Patterson, MD

Preface

The goal of this book is to provide practicing surgical pathologists, dermatologists, cutaneous oncologists, Mohs' surgeons, and dermatopathologists with a single volume that reviews the clinical and pathologic features of rarely encountered cutaneous neoplasms. We have attempted to include an in-depth discussion of the clinical findings, as well as the histologic and (when required) immunopathologic features of these diseases. Additional data used to make and support the diagnoses is discussed for each entity as well as the prognostic parameters and some therapy notes.

The book is organized into general categories correlating with the cell(s) of origin for each group of neoplasms. The first section covers rare epidermal tumors. In this section, we discuss carcinomas that are not commonly encountered, foregoing any discussion of the very well known and described common tumors. A related chapter dealing with rare tumors of the cutaneous appendages follows. Subsequent chapters addressing rarely encountered melanocytic neoplasms, mesenchymal neoplasms (including those of soft tissue origin, muscle, and bone), neural and neuroendocrine tumors, and hematopoietic neoplasms involving the skin are followed by tumors that metastasize to the skin. For each entity, we have attempted to provide an atlas of clinical manifestations that will serve as a "bed-side" clinical reference, followed by a series of photomicrographs depicting the histologic changes. In all cases, recent updates on molecular tools helpful in attaining the diagnosis are added to the sections on histology and immunohistochemistry.

Many cutaneous neoplasms represent a part of a syndrome, often serving as the presenting feature. In such cases, the syndromes are explored in greater detail, with descriptions extending beyond the cutaneous lesions.

The underlying goal of the book is to serve as a useful reference book for all physicians that care for patients with cutaneous neoplasms. These cutaneous neoplasms may not even be well known to physicians specializing in skin disorders. It is our hope that the presentation of clinical photographs of rare entities and accompanying histologic photomicrographs will help such clinicians to arrive at appropriate pathologic diagnoses with resultant appropriate management. We hope that this volume will result in better diagnoses of such rarely encountered cutaneous tumors, and ultimately to better treatments and outcomes for our patients.

The authors have many friends and colleagues to thank for the creation of this work that centers exclusively on esoteric clinical entities. Dr. Rongioletti

would like to thank his coeditors, Bruce and Irina, for their dedication and efforts in the realization of this project; all the contributors for their expertise, hard work, and commitment; all the colleagues and friends for their encouragement; and his loving ladies, his mother and his perpetual fiancée, for their sweetness and patient. Dr. Smoller would like to express his sincere gratitude to Drs. Sara Shalin and Jerad Gardner, both from the University of Arkansas for Medical Sciences, for their help in writing the manuscript and with finding many of the clinical pictures included in the volume. He would also like to express his extreme thanks to and love for his wife, Laura, whose undying patience allows him the time to allocate to endeavors such as writing this book. Dr. Irina Margaritescu would like to thank her family for their unconditional love and support. She would like to dedicate this book to them and especially to her precious little boy, Alexandru-Vlad. We all would like also to thank Richard A. Hruska for his support. If a doctor in any part of the world makes a correct diagnosis after looking at a picture or treat a patient in a proper way after reading a chapter or just a few lines of this book, our efforts have been well rewarded.

Genova, Italy

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Part I

Tumours of the Epidermis

Adenoid (Acantholytic) Squamous Cell Carcinoma

1

Valentina Caputo and Franco Rongioletti

Introduction

Cutaneous acantholytic squamous cell carcinoma (ASCC) was initially described in 1947 by Lever as a tumor composed of both solid and gland-like epithelial nests and was called adenoacanthoma of the sweat glands. He later revised his classification, and actually, ASCC is considered an uncommon, distinctive variant of squamous cell carcinoma, characterized by a typical SCC pattern in combination with acantholytic pseudoglandular space formation. Although ASCC is considered as a more aggressive variant of SCC, its prognosis seems mostly to be more related to the characteristics of the host and the grading of tumor rather than the histopathological features.

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Clinical Features

ASCC generally presents as a reddish, scaling, often cup-shaped, and ulcerated lesion on sun-exposed areas of elderly patients, predominantly on the head (Fig. 1.1) and neck, although other sites such as the vulva, penis, breast, foot, leg, and arm can be involved. It is more common in males than females, with a mean age at diagnosis of 70 years.

Pathology

Histologically, the tumor is composed of cords and nests of atypical keratinocytes with an infiltrative pattern of growth. Connection to the overlying epidermis, which may show hyperkeratosis and parakeratosis, is present in most cases, even if sometimes it may be only focal or absent (Fig. 1.2). Many of the tumor cells may show tubular, alveolar, and pseudoglandular arrangement. The hallmark of the lesion is the pseudogland, which is an open space lined by atypical flat, cuboidal, or cylindrical cells (Fig. 1.3). The space usually contains isolated acantholytic necrotic cells floating within the lumen (Fig. 1.4). The epithelial cells are atypical with bright eosinophilic, focally glassy cytoplasm arranged in loose cohesive clusters representing pseudoacantholysis (Fig. 1.5). ASCC stains positively for

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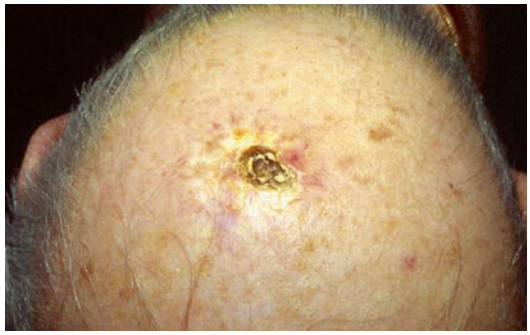

Fig. 1.1 A keratotic nodule with erythematous halo on the scalp of an old patient

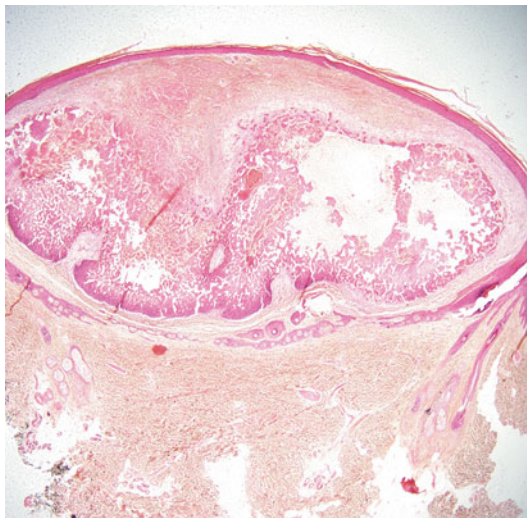

Fig. 1.2 A squamous tumor extending into the dermis with pseudoglandular spaces and necrotic areas

immunohistochemical markers towards pankeratin and epithelial membrane antigen (EMA), but immunostains for carcinoembryonic antigen (CEA) give invariably negative results. In the literature, a decreased expression of intercellular adhesion proteins, such as of Dsg3, E-cadherin, and syndecan-1, has been described in ASCC compared to conventional SCC, and it has been suggested that this may contribute to the development of acantholysis and of the controversially more aggressive biological behavior.

Acantholytic cells may appear extremely bizarre, large, with glassy eosinophilic cytoplasm. Nuclei may vary from atypical to pleomorphic and may be single or multiple, and mitotic figures are variably present.

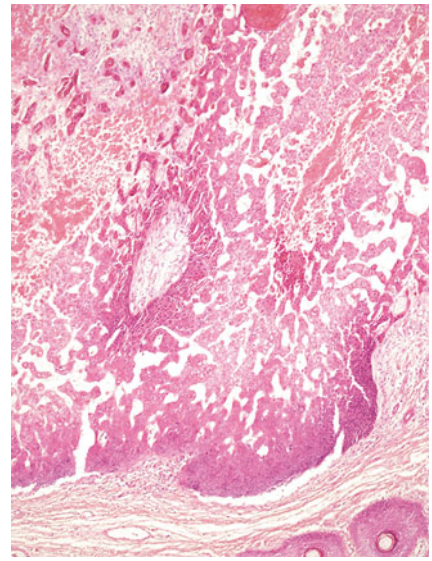

Fig. 1.3 Pseudovascular or pseudoglandular appearance due to tumor cell discohesiveness and necrosis

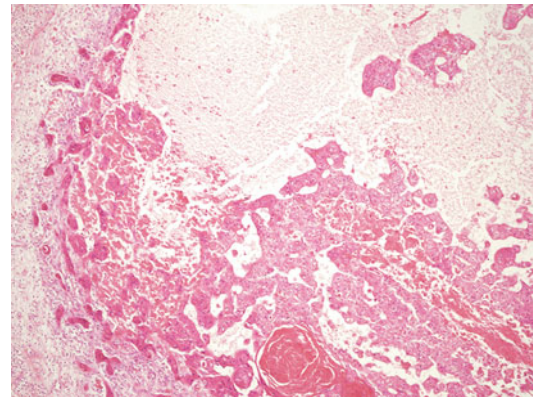

Fig. 1.4 Lining is composed of squamous epithelium and spaces with necrotic debris, keratin, and keratinous cyst

Differential Diagnosis

Differential diagnosis is only histological and is directed mainly towards gland-forming malignancies, as eccrine adenocarcinoma, adenosquamous carcinoma, and metastatic adenocarcinoma. Another important differential diagnosis concerns epithelioid angiosarcoma. In eccrine adenocarcinoma as in adenosquamous carcinoma, the glandular spaces are lined with periodic acid–Schiff (PAS)-positive cells, whereas in ASCC,

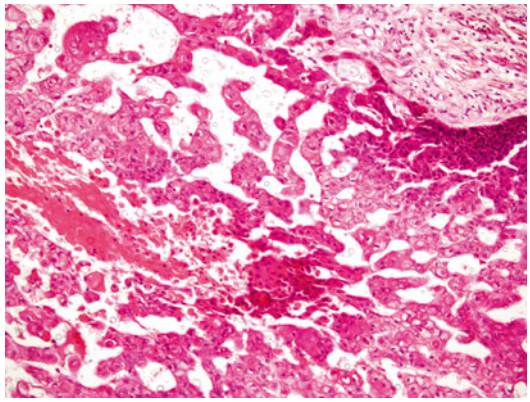

Fig. 1.5 The epithelial cells are atypical with bright eosinophilic, focally glassy cytoplasm arranged in loose cohesive clusters representing pseudoacantholysis

the cells are PAS negative. Moreover, ASCC shows no mucin secretion, and pseudoglandular spaces are due to acantholysis, not to real glandular differentiation, and tumor cells in ASCC lack the immunohistochemical positivity to CEA, S100 protein, and keratin 7 that can be seen in glandular malignancies. In epithelioid angiosarcoma, the vascular spaces contain red blood cells and not acantholytic keratinocytes, although cases of ASCC containing red blood cells within the pseudoglandular spaces have been notoriously described. In these cases, immunohistochemical stains are required. Angiosarcomas are typically positive for vimentin and CD-34, whereas ASCC shows positivity for cytokeratin and EMA.

Prognosis

It is difficult to assess the real biological behavior and metastatic potential of ASCC, because of the lack of adequate data regarding tumor size and site and circumstances of the patients in several of the largest published series. In the literature, the recurrence and metastasis rates reported are variable and range from 6 % to 10 % and from 2 % to 43 %, but, according to a recent analysis, the aggressive biological behavior of ASCC seems to correlate more with factors such as tumor size greater than 1,5 cm, recurrence, site of involvement, infiltration depth >3 mm, immunosuppression, and radiation therapy rather than with histopathological features. Moreover, recurrent tumors and metastases do not always reproduce the adenoid pattern of origin.

Treatment

The treatment and follow-up of the patients should be similar to that for conventional SCC. Early wide surgical excision of the tumor has to be considered the treatment of choice.

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Clear Cell and Signet-Ring Cell Squamous Cell Carcinoma

2

Irina Margaritescu and A. Doru Chirita

Introduction

Clear cell squamous cell carcinoma (clear cell SCC) was first described by Kuo in 1980 as a rare variant of squamous cell carcinoma (SCC). It appears predominantly on sun-exposed sites in elderly. The neoplasm is formed by sheets or islands of clear cells with empty-appearing or "bubbled" cytoplasm. Signet-ring cell squamous cell carcinoma (signet-ring cell SCC) is a very rare histopathological variant of SCC with only a few cases reported. It can be exceedingly difficult to differentiate this neoplasm from both primary cutaneous and secondary adenocarcinomas.

Clinical Features

The lesions of clear cell SCC and signet-ring cell SCC appear as nodules or ulcerated tumors on sun-exposed areas, especially on the head and neck region of elderly people with chronic sun exposure (Fig. 2.1).

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Pathology

Originally, Kuo described three types of clear cell SCC, namely, keratinizing (type I), nonkeratinizing (type II), and pleomorphic (type III). Type I tumors are described as neoplasms formed by sheets or islands of clear cells with empty-appearing or "bubbled" cytoplasm with foci of keratinization and keratin pearl formation. Type II tumors are described as predominantly dermal neoplasms with parallel and anastomosing cords of cells with central nuclei and finely reticulated clear cytoplasm, without keratinization and ductal or glandular differentiation (Figs. 2.2, 2.3, 2.4, 2.5, and 2.6). In Kuo's opinion, these could represent either recurrent SCCs or primary adnexal tumors of undetermined histogenesis. Type III tumors are described as pleomorphic neoplasms with clear cells arising from the epidermis, which show foci of squamous differentiation, dyskeratotic cells, and acantholysis and considerable perineural and vascular involvement. Kuo's examples showed no evidence of either glycogen or mucin within the tumor cells which would support his hypothesis that clear cell changes are degenerative. However, in recent studies, examples of clear cell SCC have been shown to demonstrate glycogen accumulation in the cytoplasm of the clear cells. Only a few cases of authentic cutaneous signet-ring cell SCC have been reported. Apart from the areas with signet-ring cell appearance of the neoplastic intraepidermal or invasive cells, the tumors may show foci of

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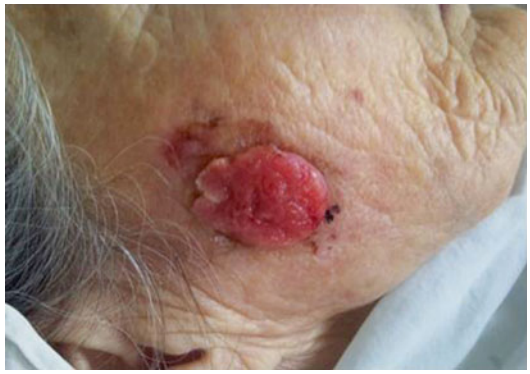

Fig. 2.1 An ulcerated vegetating tumor on the cheek of an 83-year-old woman

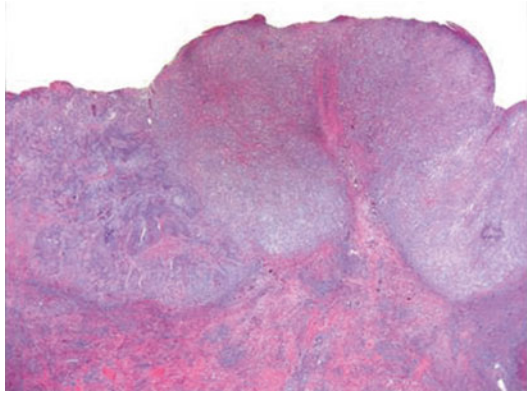

Fig. 2.2 The ulcerated epithelial neoplasm displays large areas of clear cells recognizable even at low magnification

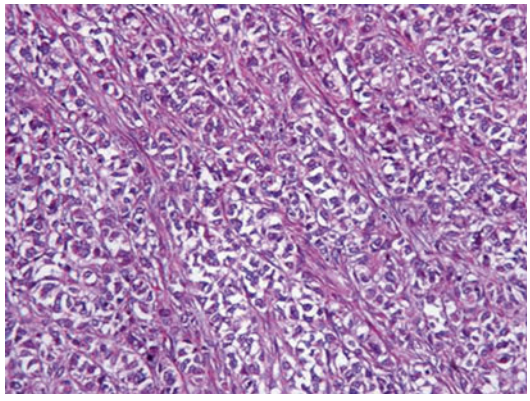

Fig. 2.3 At higher magnification, these areas show parallel and anastomosing cords of cells with central nuclei and clear cytoplasm, without keratinization and ductal or glandular differentiation

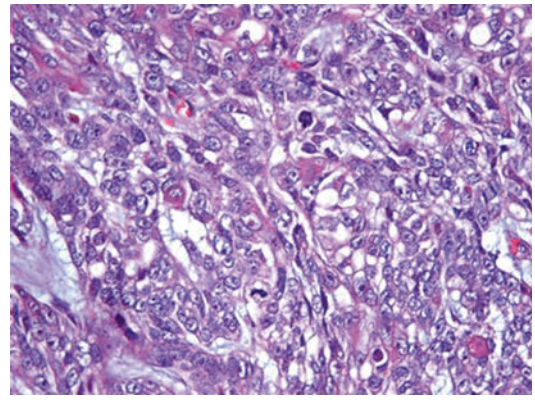

Fig. 2.4 Very focally, the cells show individual keratinization. The cells are large, with vesicular and pleomorphic nuclei and prominent nucleoli. Many mitotic figures are easily identified

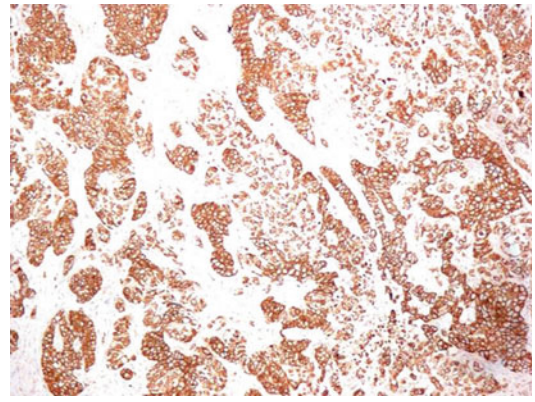

Fig. 2.5 The neoplasm, including the clear cell areas, stains positive for cytokeratin 34βE12

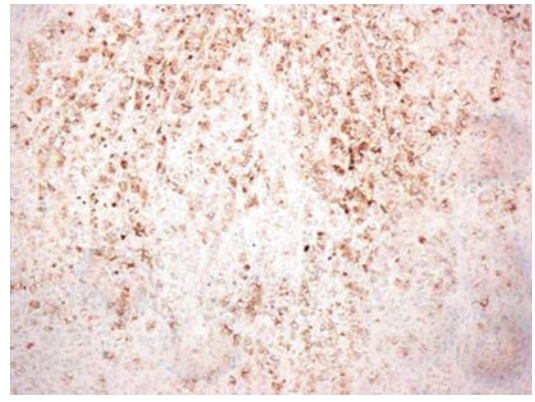

Fig. 2.6 Most of the cells are EMA positive

conventional squamous cell carcinoma that point to the real nature of the neoplasm. The results of the studied cases indicated that mechanisms responsible for the formation of the signet-ring cells are diverse. In some cases, cytosolic accumulation of glycogen was found. In other cases, intracytoplasmic material was shown to be negative for both PAS and mucicarmine.

Differential Diagnosis

SCC with extensive clear cell changes can pose difficulties in differentiation from other neoplasms with clear cells, such as clear cell acanthoma, clear cell hidradenoma, trichilemmoma, balloon cell nevus, proliferating pilar tumor, clear cell basal cell carcinoma, clear cell hidradenocarcinoma, clear cell porocarcinoma, sebaceous carcinoma, clear cell atypical fibroxanthoma, balloon cell melanoma, and metastatic renal cell carcinoma. The presence of more typical areas of SCC (foci of squamous differentiation with horn cyst formation) and identification of a preexisting lesion of actinic keratosis or Bowen's disease should enable the pathologist to establish a correct diagnosis. Clear cell basal cell carcinoma (BCC) is differentiated by the presence of typical areas of BCC with peripheral palisading and retraction artifact. Unlike SCC with clear cells, the rare examples of authentic trichilemmal carcinoma display true trichilemmal differentiation (peripheral columnar cells with clear cytoplasm arranged in a palisade resting on a hyaline basement membrane). Identification of ductal structures by histology and immunohistochemistry (EMA and CEA) allows separation of clear cell hidradenocarcinoma or clear cell porocarcinoma from clear cell SCC.

Signet-ring cell cutaneous SCC should be differentiated from primary cutaneous or secondary adenocarcinomas using special stains (PAS-D, mucicarmine), immunohistochemistry (EMA, CEA, etc.), and clinical data.

Prognosis

Due to the rarity of these variants of SCC, it is difficult to ascertain its malignant potential. The prognosis depends especially on the tumor size, degree of differentiation, and the presence of intravascular and perineural invasion.

Treatment

Complete surgical excision of the tumor is the treatment of choice.

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Squamous Cell Carcinoma with Mucinous Metaplasia

3

Valentina Caputo and Franco Rongioletti

Introduction

Squamous cell carcinoma with mucinous metaplasia (SCCMM) is an invasive, atypical squamous cell proliferation containing mucin-producing, "signet-ring"-shaped cells. SCCMM differs from adenosquamous carcinoma and mucoepidermoid carcinoma by the absence of glandular structures and of a definite adenoid pattern. It is a very rare neoplasm with only three cases reported in the literature, one associated with high-risk HPV type 18. Mucin is not a normal product of adult keratinocytes. It has been argued that the influence of environmental factors, as HPV infection and viral genomic integration, could trigger a bipotent keratinocyte progenitor to differentiate along two different functional pathways, generating squamous or mucin-producing cells, progressively and irreversibly losing its original proliferative capacities and undergoing a sort of differentiative and replicative senescence with mucin production.

Clinical Features

SCCMM has been described as a reddish, scaling, nodular, warty lesion of the head and neck region of elderly patients, although one case has been reported in the sole.

Pathology

The tumor is characterized by an invasive SCC with large vacuolated cells, filled with mucin resembling "signet-ring cells," scattered throughout the full epithelial thickness and in intimate association with the atypical squamous component (Figs. 3.1, 3.2, and 3.3). There are no glandular structures or adenoid growth pattern. The presence of intracytoplasmic mucin is confirmed by positive staining for Alcian blue and colloidal iron (Fig. 3.4), while PAS and PAS diastase are negative. Both the squamous and the mucinous cells are characterized by nuclear pleomorphism, with densely packed chromatin, and result strongly positive with cytokeratin AE1/AE3 , weakly positive with EMA and CK5/6, while CK7, CK20, CEA, BerEP4, S100, Her2-neu, and ER are negative. Weak nuclear and cytoplasmic p16 immunoreactivity in both cellular populations of the tumor

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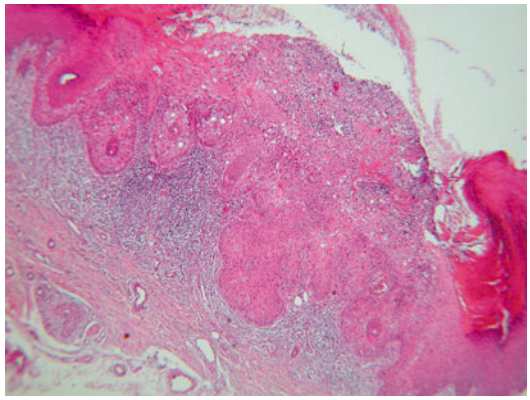

Fig. 3.1 Squamous cell carcinoma with mucinous metaplasia. The tumor is characterized by an invasive SCC with large vacuolated cells scattered throughout the full epithelial thickness without glandular structures

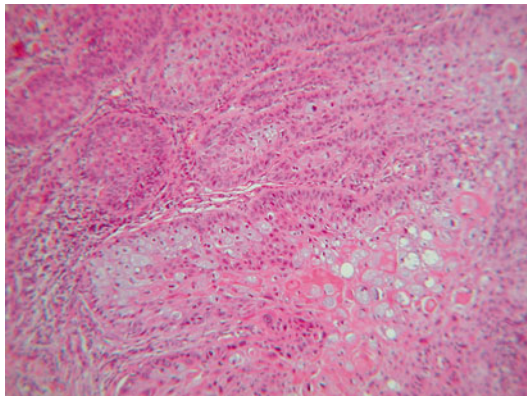

Fig. 3.2 Squamous cell carcinoma with mucinous metaplasia. Large vacuolated cells are in intimate association with the atypical squamous component

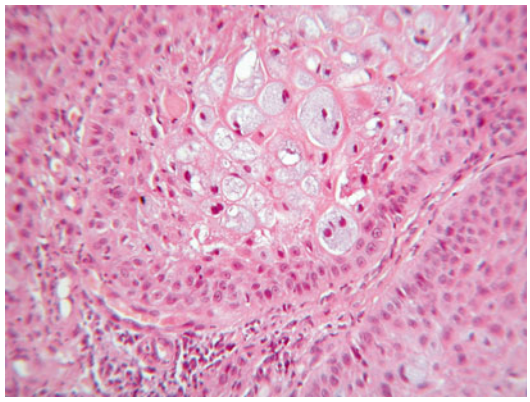

Fig. 3.3 Squamous cell carcinoma with mucinous metaplasia. Large mucinous cells inside the squamous proliferation

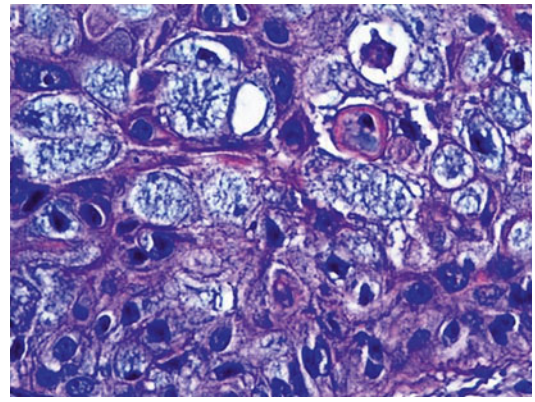

Fig. 3.4 Squamous cell carcinoma with mucinous metaplasia. The presence of intracytoplasmic mucin is confirmed by positive staining for colloidal iron

and the presence of oncogenic high-risk HPV 18, by real-time PCR, has been described in one case.

Differential Diagnosis

Histopathologic differential diagnosis includes skin tumors exhibiting mucin-containing cells, mainly adenosquamous carcinoma and mucoepidermoid carcinoma. Both are characterized by the presence of glandular structures, invariably positive for CEA and CK7, while mucinous cells of SCCMM have been reported negative because they are keratinocytes.

Other differential diagnoses to be considered are acantholytic SCC that is characterized histopathologically by a pseudoglandular pattern due to acantholysis of keratinocytes, with absence of mucin-secreting cells, and extramammary Paget disease. The main feature that rules out Paget disease is the atypia of both the squamous and the mucin-secreting component, while in Paget disease the keratinocytes are cytologically benign.

Prognosis

SCCMM is an indolent, often superficially invasive neoplasm. The few cases reported in literature did not show recurrence or metastases to lymph nodes.

Treatment

Surgical excision is the treatment of choice.

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Adenosquamous Carcinoma

4

Valentina Caputo and Franco Rongioletti

Introduction

Adenosquamous carcinoma (ASC) of the skin is a rare, distinctive, usually aggressive neoplasm, characterized by a component of conventional squamous cell carcinoma merging with a component of adenocarcinoma with true glandular formation. It was initially described in 1985 by Weidner and Foucar, although this term has been erroneously used for tumors with better prognosis as mucoepidermoid carcinoma and adenoid (acantholytic) squamous cell carcinoma. More than 40 cases have been reported in the literature, mostly as single cases or small series.

Clinical Features

Most of the reported cases arise on sun-damaged skin areas such as the face and the scalp (70 %) or the upper extremities (15 %) (Fig. 4.1) of elderly patients (mean age 74 years) with a male predominance (70 %). The penis is also an unusual reported site. ASC usually appears as elevated, indurated, keratotic plaques or nodules, often ulcerated, ranging from 1 to 6 cm in size, without clinical distinguishing features.

Pathology

ASC is a biphasic tumor with an epithelial malignant component of conventional SCC, merging with an epithelial malignant component of adenocarcinoma (Figs. 4.2 and 4.3). Histopathologically, the tumor consists of interlacing nests and cords of atypical squamous cells forming keratocysts and showing superficial epidermal connection, indicative of an epidermal origin. The adenocarcinomatous component ranges from focal to diffuse and consists of glandular and cystic spaces lined by cuboidal to low-columnar mucin-secreting epithelium containing mucicarmine and Alcian blue-positive material. A helpful histopathologic clue is the presence within glandular lumens of neutrophils and cellular necrotic debris. Perineural invasion is reported in 15 % of primary tumors and in 43 % of recurrences. Recurrent disease tends to occur in younger patients (mean age 65 years) and more frequently involves the face (43 %). There is a progressive transition and merging of the two cellular components, characterized by a keratin 7-/CEA + immunoprofile in the squamocellular

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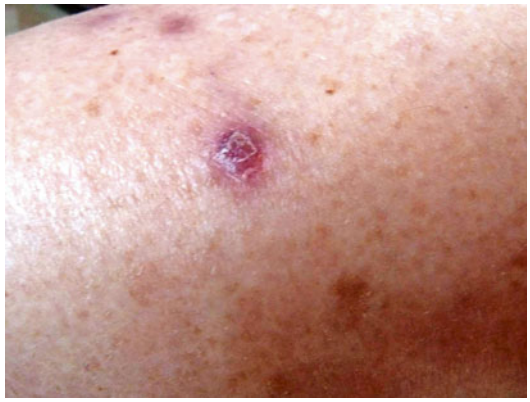

Fig. 4.1 Adenosquamous carcinoma. An erythematous nodule with erosive surface on the upper arm

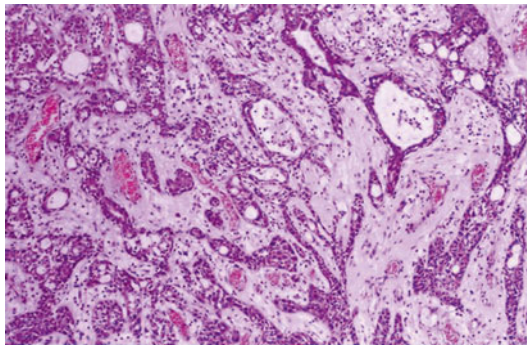

Fig. 4.2 The tumor consists of interlacing nests and cords of atypical squamous cells with glandular and cystic spaces

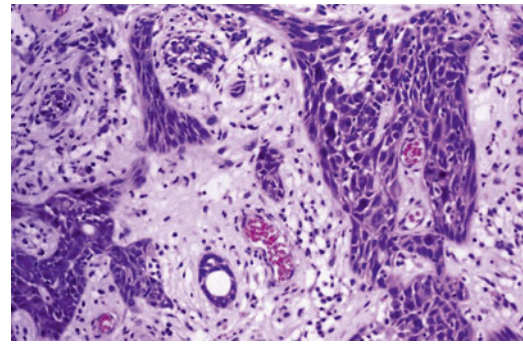

Fig. 4.3 The epithelial cords contain glandular lumens with clusters of mucin-secreting clear cells

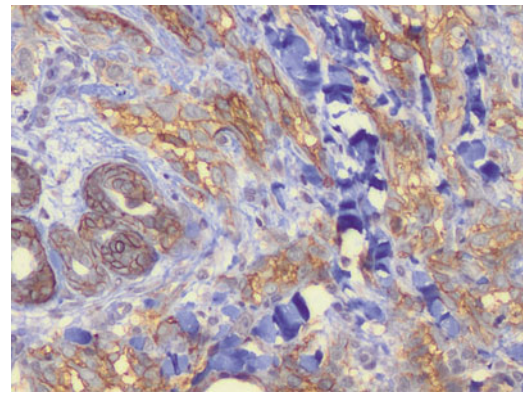

Fig. 4.4 The adenocarcinomatous component is stained by CEA

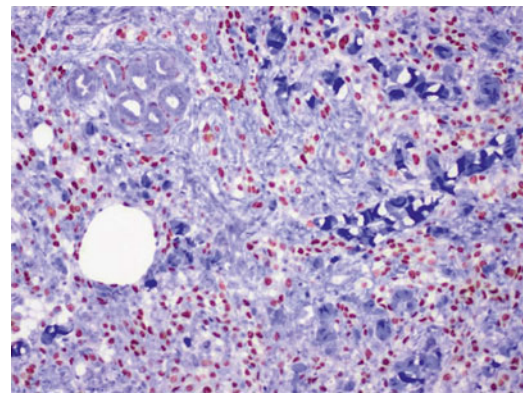

Fig. 4.5 Both the squamous and glandular components stain positively with p63

counterpart and keratin 7+/CEA + immunoprofile in the adenocarcinomatous counterpart (Fig. 4.4). Both the squamous and glandular components stain positively with p63 (Fig. 4.5) and cytokeratin 5/6, suggesting a primary cutaneous origin.

Differential Diagnosis

ASC should be histologically distinguished mainly from mucoepidermoid carcinoma. Although some authors consider ASC and mucoepidermoid carcinoma as the opposite extremities of a spectrum of the same entity, mucoepidermoid carcinoma shows slight different features consisting of low-grade appearing squamous cells intermingled with intermediate clear cells and mucin-secreting goblet cells. SCC with mucinous metaplasia is characterized by a component of conventional SCC with mucinous, PAS-positive, and Alcian blue-positive cells, not arranged in glandular spaces.

Another differential diagnosis is with acantholytic squamous cell carcinoma that is characterized by pseudoglandular spaces due to acantholysis of dyskeratotic keratinocytes in the absence of true glandular formation and mucin-secreting cells. Invasive Bowen's disease may show glandular differentiation, but ASC does not show typical changes of Bowen's disease in the epidermis. Cutaneous metastases of visceral ASC may enter the differential diagnosis, but recently it has been reported that primary cutaneous neoplasms are diffusely p63 and cytokeratin 5/6 positive.

Prognosis

ASC is considered as high-risk subtype of SCC, with a propensity for local invasion, multiple recurrences, and nodal metastases. Tumor thickness and perineural invasion have to be considered high-risk histopathological features, predictive of tumor persistence and local recurrence. Immunosuppression, especially in organ-transplanted patients or in patients affected by chronic lymphocytic leukemia, is an important clinical risk factor for a more aggressive behavior.

Treatment

Although Mohs micrographic surgery is considered the best initial treatment, the risk of locoregional recurrence is high and patients should be carefully monitored. For locally advanced disease, especially in cases with perineural invasion, postoperative radiation therapy is recommended, while adjuvant radiotherapy may be considered, but its effectiveness has still to be assessed definitely. In cases requiring palliation therapy, the use of cetuximab, a recombinant human and murine chimeric antibody against the epidermal growth factor receptor, is suggested, but its efficacy is still under investigation.

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Mucoepidermoid Carcinoma

5

Valentina Caputo and Franco Rongioletti

Introduction

Mucoepidermoid carcinoma (MEC) is a malignant epithelial neoplasm characterized by a proliferation of epidermoid, intermediate and mucous, columnar and/or clear cells in varying proportions. MEC is one of the most common cancers arising in major and minor salivary glands, accounting approximately for 30 % of all malignancies. It has been reported also in other anatomic sites, especially of the head and neck, arising from exocrine glands of the upper aerodigestive tract and tracheobronchial tree. Exceptional cases affecting the thyroid gland and the breast have been described. Primary cutaneous MEC is extremely rare with only 11 cases reported in literature, and the possibility of a cutaneous metastasis should be always ruled out. The indiscriminate use as synonyms of the term mucoepidermoid and adenosquamous to designate carcinomas with a biphasic differentiation, both squamous and glandular, has been a source of confusion. The importance of separating the two entities is not only semantic but clinical, since ASC often shows an aggressive biological behavior with locoregional recurrence and metastatic potential, while MEC is an indolent neoplasm. On this basis, some authors have proposed a spectrum of disease, with MEC at the low-grade end and ASC at the high-grade end. On the contrary, a recent review outlines the unpredictable behavior and the metastatic potential of MEC, stating that there is no reason to believe that MEC of the skin and MEC of salivary glands with similar pathological grade have a different biological behavior. Another debate concerns the classification of cutaneous MEC that is identical to the salivary counterpart. The skin, breast, and salivary glands share a common embryogenesis, deriving from the surface ectoderm, and are characterized by proliferation and further differentiation of tubuloglandular structures in the underlying mesenchyme. For this reason, MEC has been considered as a tumor of cutaneous appendages, with an adnexal rather than epidermal origin.

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Clinical Features

MEC usually arises as a skin nodule, dermal based, solid, or cystic, sometimes ulcerated (Fig. 5.1), with predilection for head and neck regions and acral extremities. Almost all patients reported in literature were over the age of 50 years at time of diagnosis, with the exception of a case reported in a child, with a slight prevalence in males.

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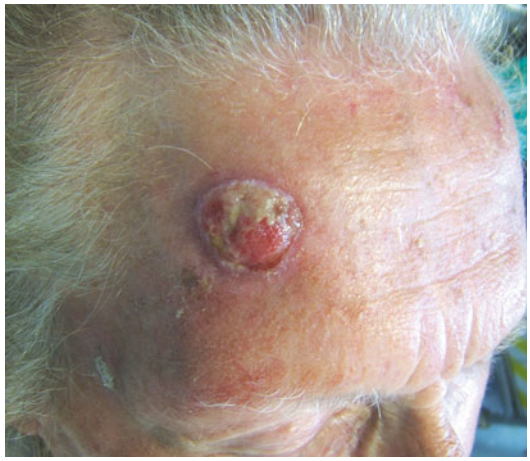

Fig. 5.1 Mucoepidermoid carcinoma. An ulcerated nodule on the forehead of an old patient

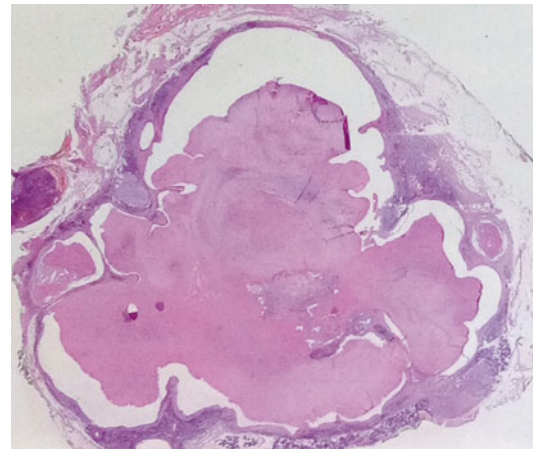

Fig. 5.2 Mucoepidermoid carcinoma. A dermal-based epithelial neoplasm with solid-cystic component in the absence of epidermal connection

Pathology

MEC is usually a dermal-based nodular, nonencapsulated solid, and/or cystic neoplasm without continuity with the overlying epidermis (Fig. 5.2). It is characterized by proliferation of squamous, intermediate, mucin-secreting columnar and/or clear cells with gland formation in varying proportions (Figs. 5.3 and 5.4). On the basis of the histopathologic features, including pattern of growth, nuclear atypia and cellular differentiation, presence of mucous cells, and glands formation, this tumor is subdivided in low, intermediate, and high grade. Peritumoral fibrosis is a common feature. Mucin stains such as mucicarmine and Alcian blue highlight the mucin-secreting cells (Fig. 5.5) and the content of glandular and cystic spaces, while immunohistochemistry for CEA, EMA, (Fig. 5.6) and CK7 results strongly positive in the mucinous and glandular cells. The immunohistochemical staining for p63 gives positive result in primary cutaneous MEC and is helpful in differentiating cutaneous metastatic MEC.

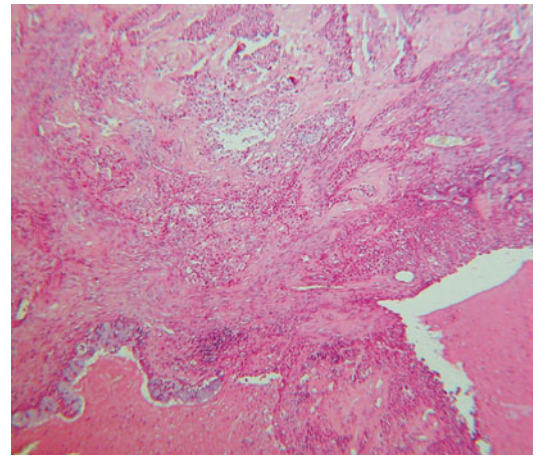

Fig. 5.3 Mucoepidermoid carcinoma. An atypical squamous dermal proliferation with ductal structures

Differential Diagnosis

MEC should be distinguished mainly from adenoid squamous carcinoma (ASC). Although some authors consider ASC and mucoepidermoid carcinoma as the opposite extremities of a spectrum of the same entity, the latter is characterized by a mixture of neoplastic epidermoid cells, mucus-secreting cells, and intermediate epithelial cells differently from ASC that shows a component of invasive SCC, merging with a component of adenocarcinoma with true glandular differentiation. SCC with mucinous metaplasia is characterized by a component of conventional SCC with mucinous, PAS-positive, and Alcian blue-positive cells, not arranged in glandular spaces. Another differential diagnosis is with acantholytic squamous cell carcinoma that is characterized by pseudoglandular spaces due to acantholysis of

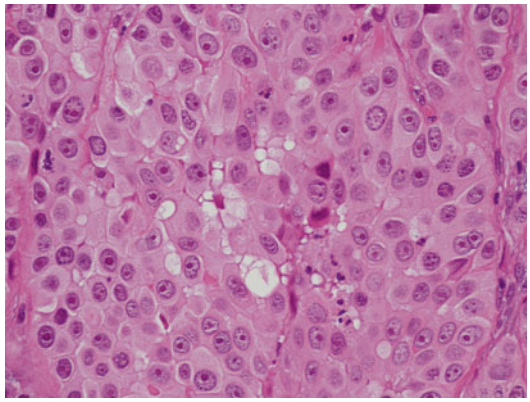

Fig. 5.4 Mucoepidermoid carcinoma. The proliferation is made of atypical epidermoid, clear cells, and mucinous cells

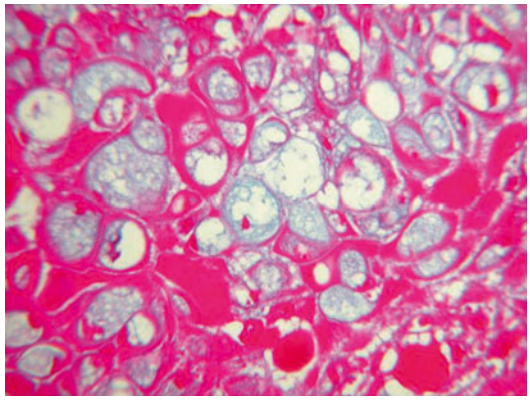

Fig. 5.5 Mucoepidermoid carcinoma. Mucin-secreting cells are stained by Alcian *blue* stain

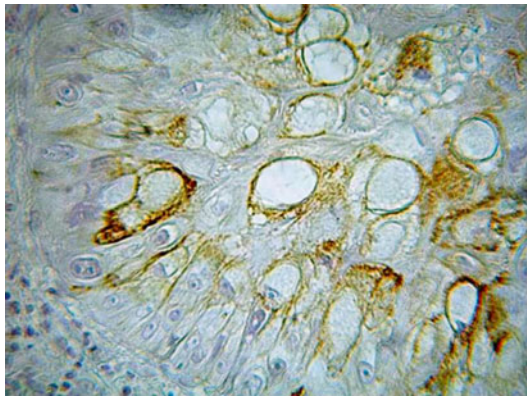

Fig. 5.6 Mucoepidermoid carcinoma. EMA results positive in the mucinous cells

dyskeratotic keratinocytes, in the absence of true glandular formation and mucin-secreting cells. Mucinous metaplasia in nonneoplastic processes, like mucinous syringometaplasia, is an uncommon finding and a challenging diagnosis, and it is important to be aware of its existence. Cutaneous metastases from a distant MEC may enter the differential diagnosis with primary cutaneous MEC, but it has been reported that the last ones are diffusely p63 positive. Moreover, despite primary cutaneous MEC being low to intermediate grade, metastatic cases are often high-grade neoplasms.

Prognosis

Most reported cases are low-grade neoplasms with favorable outcome after adequate excision; only rarely cases of high-grade tumors with aggressive behavior resulting in the death of the patient have been reported. On this basis, it is reasonable to believe that prognosis mostly depends on pathological grade and that cutaneous MEC most likely behaves similarly to its salivary gland counterpart.

Treatment

Complete surgical resection is expected to be the treatment of choice in low-/intermediate-grade MEC. A presumptive case of high-grade MEC was treated successfully by Mohs micrographic surgery. Recurrence after excision occurs up to 50 % of high-grade MEC and up to 12.2 % of low-grade MEC.

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Carcinosarcoma

6

Valentina Caputo and Franco Rongioletti

Introduction

Carcinosarcoma of skin (CS) is an extremely rare biphasic neoplasm composed of intimately admixed malignant epithelial and mesenchymal elements. These tumors occur more frequently in the internal organs such as the female and male genital tracts, gastrointestinal tract, lungs, breast, upper and lower urinary system, oronasopharynx, larynx, thyroid, and thymus. Occurrence in the skin is extremely rare. Only about 40 cases have been reported in literature, mostly as single cases or small series. Different theories have been proposed to explain the pathogenesis of CS: a collision tumor of two unrelated tumors, a combination of two divergent cell lines from a single stem cell, and a metaplastic transformation of part of the carcinoma into a sarcoma.

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Clinical Features

Epidermal-derived CS arises on the sun-damaged skin of the head and neck of elderly males (mean age 72 years), while adnexal CS occurs in younger patients (mean age 58 years) and may involve any site. Most of these neoplasms present as a polypoid or exophytic mass of variable color, often with overlying ulceration. The duration before clinical presentation ranges from several weeks to 30 years, with many patients reporting a recent period of fast growth.

Pathology

CS is a biphasic tumor with an epithelial malignant component admixed with a mesenchymal one. The epithelial component is represented by epidermal-derived tumors, mainly basal (Fig. 6.1a, b) or squamous cell carcinoma, or by malignant adnexal tumors such as malignant pilomatrixoma, spiradenocarcinoma, eccrine porocarcinoma (Fig. 6.2a–c), matrical carcinoma, trichilemmal cystic carcinoma, and Merkel cell carcinoma. The mesenchymal component may be homologous or heterologous. The former consists of spindle cells with pleomorphic nuclei, necrosis, and numerous atypical mitoses, while the latter is represented by osteosarcoma, chondrosarcoma, leiomyosarcoma, rhabdomyosarcoma, and undifferentiated sarcoma. There is a progressive transition and merging of the two

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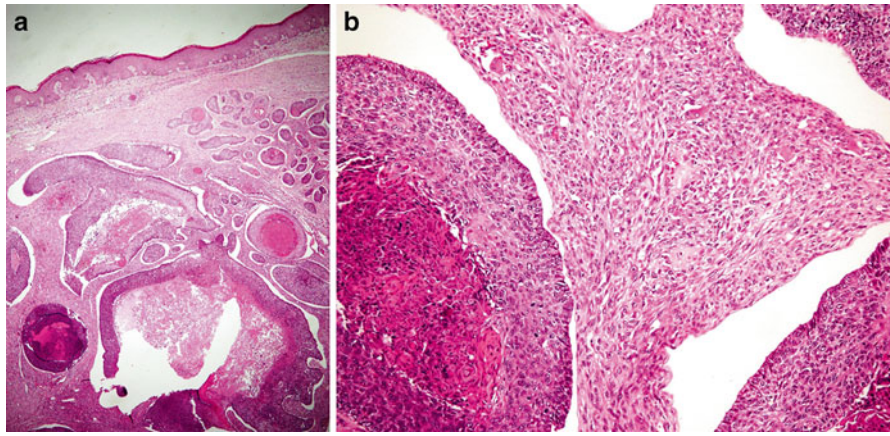

Fig. 6.1 Carcinosarcoma. (**a**) The epithelial component with features of basal cell carcinoma admixed with the mesenchymal fibrosarcomatous component. (**b**) Close-up of the pleomorphic sarcomatous and carcinomatous components

cellular components, characterized by a mostly keratin+/vimentin-immunoprofile in the epithelial counterpart and keratin-/vimentin + immunoprofile in the mesenchymal counterpart.

A combination of wide spectrum cytokeratin, glandular epithelial markers, and p63 (Figs. 6.2d, e) is helpful in the distinction of CS from other spindle cell neoplasms, while immunohistochemistry for smooth muscle actin, desmin, and myogenin may be useful in confirming smooth or skeletal muscle differentiation.

CD10 and podoplanin (D2-40) have diagnostic utility in differential with atypical fibroxanthoma that shows a strong and diffuse positive pattern of staining, while CS is negative. High proliferative index with Ki67 is easy to find in both components (Fig. 6.2f).

Identical mutations of both the tumor suppressor gene p53 and patched gene (PTCH1) have been reported in both the epithelial and the mesenchymal components, suggesting a clonal origin of the tumor.

Differential Diagnosis

The diagnosis is only a histological one and may be challenging; CS should be distinguished from other microscopic spindle cell tumors such as atypical fibroxanthoma, spindle cell squamous cell carcinoma, and spindle cell malignant melanoma.

Cutaneous metastases of soft tissue or bone sarcomas may enter the differential diagnosis but are extremely rare, and only anecdotal cases have been reported.

Prognosis

In contrast to CS of other visceral sites, the primary cutaneous seems not to behave in a very aggressive manner, with a recurrence rate of 22 %, a metastasis rate of 22 %, and an overall mortality of 11 %. Two categories of risk seem to exist: the epidermal-derived CS with a 70 % 5-year disease-free survival and the adnexal CS with a 25 % 5-year disease-free survival. Age less than 65 years, recent growth, long-standing skin tumor, and tumor size greater than 2 cm significantly correlate with poor outcome. Metastatic lesions of CS carry a significantly poorer prognosis than primary cutaneous neoplasm.

Treatment

Complete wide surgical resection combined with regional lymphadenectomy, in the event of nodal disease, is the suggested treatment. Adjuvant

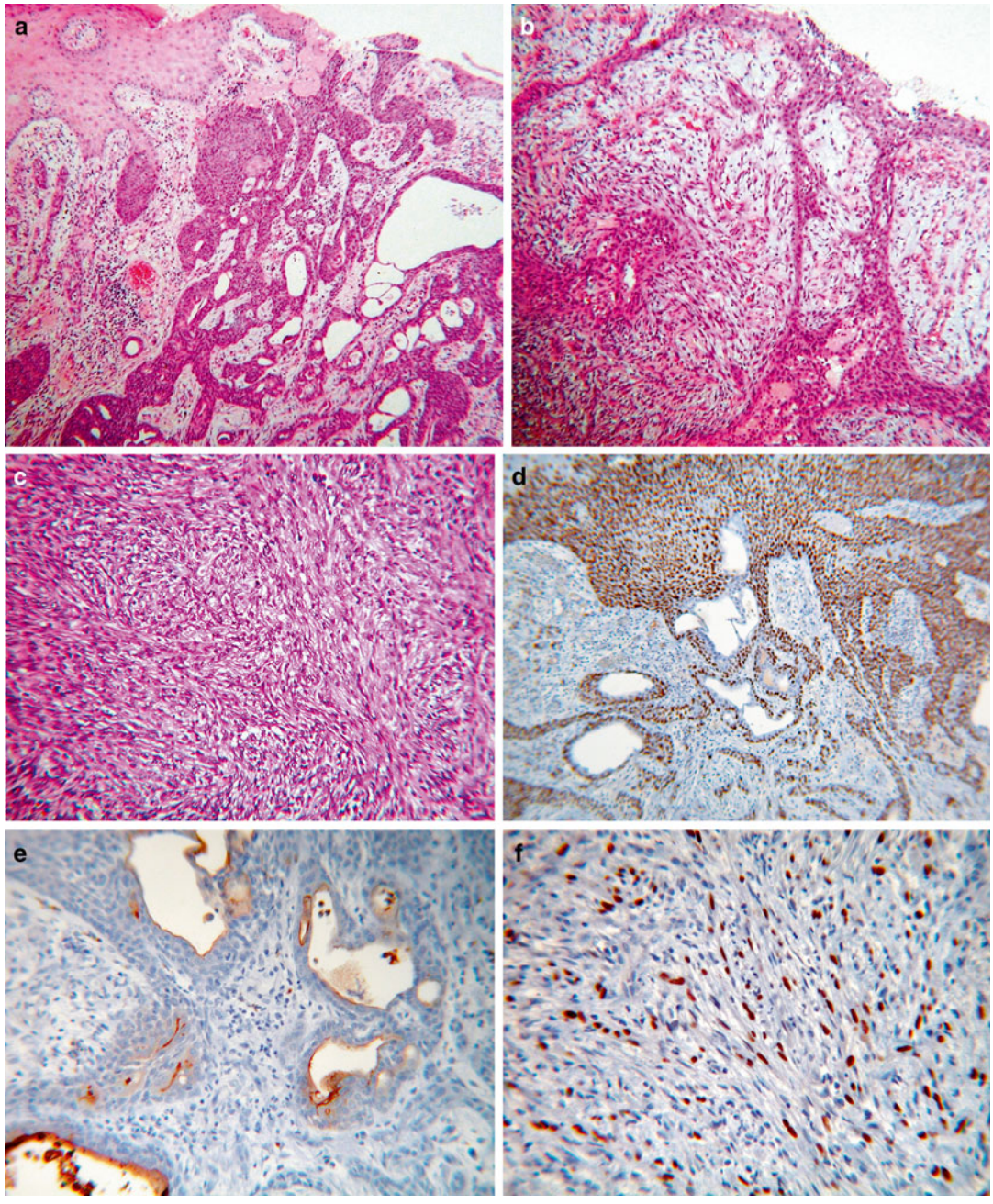

Fig. 6.2 Carcinosarcoma. (**a**) An epithelial component represented by a malignant basaloid adnexal tumor with features of porocarcinoma. (**b**) The malignant mesenchymal component admixed with the epithelial proliferation made by reticulated and irregularly anastomosing cords with ductal spaces. (**c**) The malignant mesenchymal component is made by spindle cells with pleomorphic nuclei and features of undifferentiated sarcoma. (**d**) P-63 positivity in the porocarcinomatous component. (**e**) Positive staining for CEA in the luminal ducts. (**f**) Ki-67 showing high proliferative index in the sarcomatous component

radiotherapy should be considered in patients with recurrent disease or after incomplete excision, but it has not demonstrated significant benefit.

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Lymphoepithelioma-Like Carcinoma

7

Franco Rongioletti

Introduction

Lymphoepithelioma-like carcinoma of the skin (LELCS) is a rare neoplasm of unknown etiology and low malignant potential, microscopically similar to undifferentiated nasopharyngeal carcinoma, first described by Swanson et al. in 1988.

Clinical Features

Clinically, LELCS has a predilection for sun-exposed skin of the head and neck in elderly individuals. It presents as a flesh-colored firm nodule or plaque or an erythematous or indurated lesion with a keratotic center on the face (Fig. 7.1), scalp, or shoulder of middle-aged to elderly individuals.

Pathology

Histologically, LELCS is composed of islands of enlarged atypical polygonal epithelial cells with scant amphophilic to eosinophilic cytoplasm, large vesicular nuclei, and prominent nucleoli surrounded and permeated by a dense lymphoplasmacytic infiltrate (Fig. 7.2a–c). Tumor cells are arranged in round to oval nests, isolated or anastomosing islands, trabeculae, or narrow cords. Mitotic figures ranged from 1 to 8 per high-power field. No connection to the overlying epidermis is present. LELCS exhibits immunoreactivity with high-molecular-weight cytokeratins and epithelial membrane antigen (EMA), indicating the epithelial origin. Neoplastic cells are strongly positive for CK5/6 (Fig. 7.2d), CK14, and CAM5.2 but are negative for CK19 and CK20. The surrounding lymphoid infiltrate exhibits a positive reaction with the T-cell and B-cell markers CD3 and CD20. All tumors show strong p63 protein reactivity. LELCS stains negative to EBV, in contrast to the EBV-positive staining of nasopharyngeal carcinoma. The histogenesis is unclear, although an adnexal origin is favored, with possible follicular, glandular, or sebaceous differentiation. Like undifferentiated nasopharyngeal carcinoma, LELCS could be considered to be a subtype of nonkeratinizing squamous cell carcinoma variant with an epidermal origin.

Differential Diagnosis

The histological diagnosis of LELCS may be complicated by the variable architectural pattern, the cytologic appearance of the epithelial cells, and the dense lymphoplasmacytic infiltrate that

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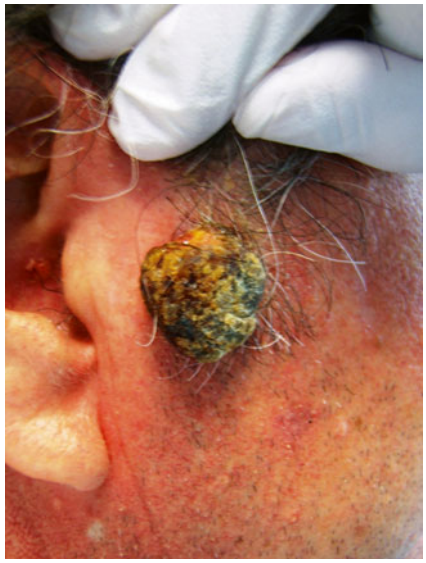

Fig. 7.1 Lymphoepithelioma-like carcinoma of the skin. An indurated lesion with a keratotic center on the face

may obscure the epithelial component. The differential diagnosis includes squamous cell carcinoma, lymphoma, pseudolymphoma, and Merkel cell carcinoma. Owing to the histological similarity to nasopharyngeal lymphoepithelioma, patients should have an otolaryngologic examination to rule out a metastatic nasopharyngeal lymphoepithelioma that is a rare but possible event, associated with a worse prognosis, with patients succumbing within a year.

Prognosis

LELCS is a tumor of low malignant potential that has a tendency toward local recurrence and very limited metastatic potential. However, metastasis to lymph nodes and internal organs, though exceptionally uncommon, may occur.

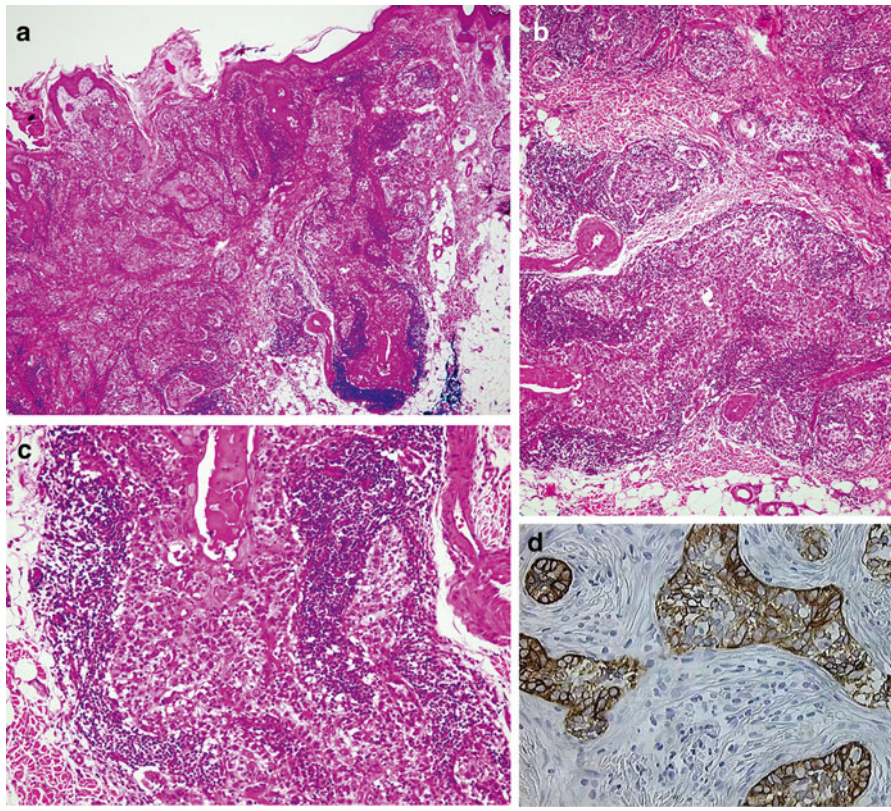

Fig. 7.2 Lymphoepithelioma-like carcinoma of the skin. (**a**) A dermal proliferation made by squamous nests in association with clusters of lymphocytes. (**b**) Squamous nests surrounded by a lymphoplasmacytic infiltrate. (**c**) Islands of enlarged atypical polygonal epithelial cells with eosinophilic cytoplasm surrounded and permeated by a dense lymphoplasmacytic infiltrate. (**d**) The epithelial islands are positive for high-molecular-weight cytokeratins

Treatment

Wide local surgical excision is the preferred treatment although radiotherapy has been used as an adjunctive treatment for aggressive, relapsing, or unresectable tumors. Mohs micrographic surgery has also been proposed for recurrent tumor with positive margins and perineural involvement.

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Part II

Tumours of Hair Follicle and Sebaceous Gland

Fibroepithelioma of Pinkus

8

Irina Margaritescu and A. Doru Chirita

Introduction

Fibroepithelioma of Pinkus (FEP), originally described by Herman Pinkus in 1953 as a "pre-malignant" variant of basal cell carcinoma (BCC), represents a rare variant of BCC with an indolent behavior which usually develops as a soft, polypoid, or nodular tumor on the lower back with a characteristic unique histology of thin anastomosing strands of basaloid and squamous cells surrounded by abundant stroma. Some authors consider FEP a fenestrated variant of trichoblastoma.

Clinical Features

It presents especially in the fifth and sixth decades of life, though the tumor may be present at any age, including in children. The lumbosacral area and the groin are the most common sites affected (Fig. 8.1). Other locations have also been reported, including the upper trunk, breast, abdomen, anus, genitalia, and sole of the foot. The tumor presents as a slowly growing, fleshy, sessile, or pedunculated lesion. It can mimic a range of benign or malignant lesions, such as a fibroepithelial polyp, pyogenic granuloma, neurofibroma, nevus sebaceous of Jadassohn, seborrheic keratosis (SK), papillomatous melanocytic nevus, or an amelanotic melanoma. It can present as a single lesion or as multiple tumors. The tumor may be solitary or may appear in association with multiple SKs or BCCs.

Pathology

The tumor is characterized by a fenestrated pattern formed by thin anastomosing strands of basaloid and squamous cells, surrounded by abundant stroma (Fig. 8.2). The strands show connection with the epidermis or preexisting infundibula and terminate in nubbins of basaloid cells with peripheral palisading (Fig. 8.3). A cleft may be present between these nubbins and adjacent fibrotic stroma. The neoplastic cells are of two types, namely, basaloid or germinative cells and more fully differentiated squamous cells with abundant pink cytoplasm (Figs. 8.4, 8.5, and 8.6). The epithelial component is embedded in an abundant loose fibrovascular stroma. Follicular germs and rudimentary follicular papillae are sometimes observed. Even rarer, signs of a more advanced follicular differentiation in the form of cornification at the isthmus may be encountered (Fig. 8.5). Not uncommonly, a nodular type of BCC may be observed in continuity with a FEP.

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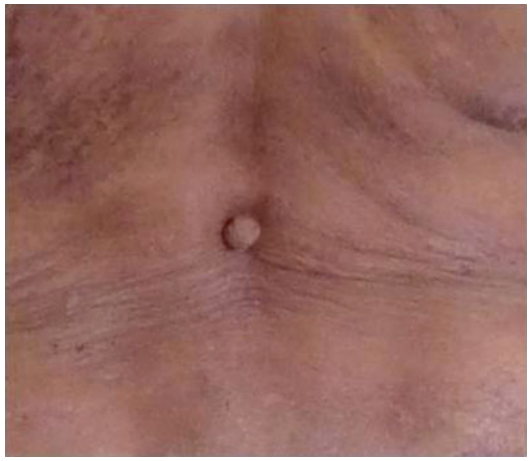

Fig. 8.1 The tumor presents as a slowly growing, fleshy, sessile, or pedunculated lesion

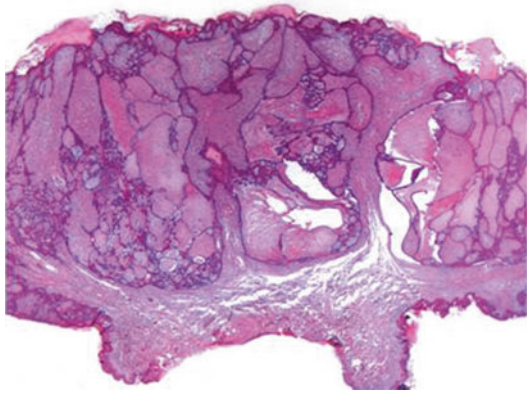

Fig. 8.2 This polypoid tumor is characterized by a fenestrated pattern formed by thin anastomosing strands of epithelial cells with multiple connections with the epidermis, surrounded by abundant stroma

Differential Diagnosis

Early lesions of FEP may be difficult to differentiate from reticulated seborrheic keratosis (SK) and tumor of follicular infundibulum (TFI). SK does not have the prominent stromal changes or the basaloid nubbins of FEP. However, FEP can appear in association with a SK. TFI is made up of columns and cords of pale squamous cells only. Eccrine syringofibroadenoma (ESFA) may superficially resemble a FEP as it also has a fenestrated pattern and a highly fibrotic stroma. However, ESFA shows eccrine ducts and no sign of follicular differentiation.

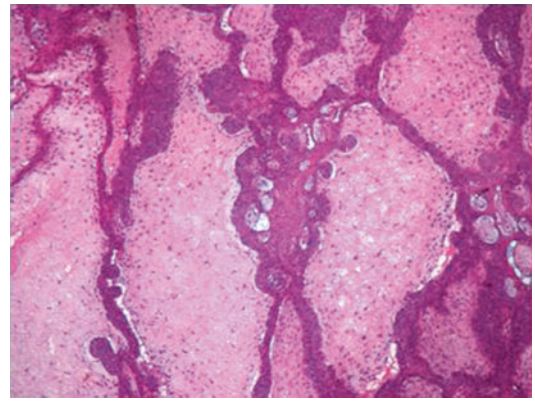

Fig. 8.3 The strands terminate in nubbins of basaloid cells with peripheral palisading that protrude into the surrounding stroma. Clefts are present between this nubbins and adjacent fibrotic stroma

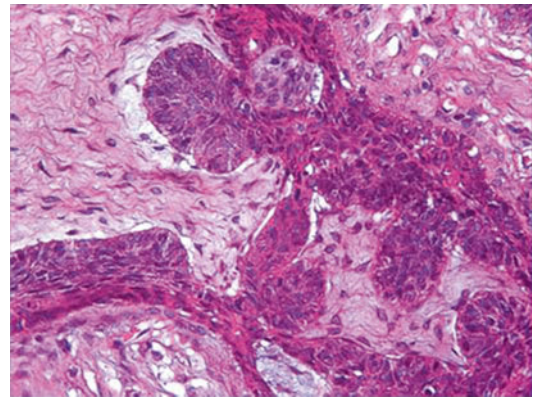

Fig. 8.4 The neoplastic cells are of two types, namely, basaloid or germinative and squamous with abundant pink cytoplasm. The follicular germ-like structures are not associated with follicular papillae

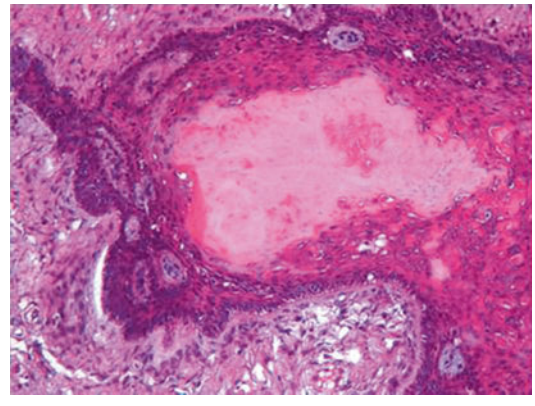

Fig. 8.5 Signs of a more advanced follicular differentiation in the form of cornification at the isthmus may be encountered

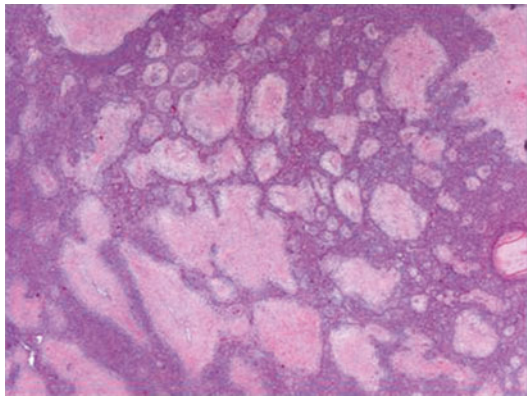

Fig. 8.6 This example of FEP shows a continuous germ made up of germinative cells that is in contiguity with a continuous papilla

Prognosis

The tumor enlarges slowly and relentlessly, but no severe destruction or metastasis has been reported.

Treatment

Complete surgical excision of the tumor is the treatment of choice. Other treatment options include curettage followed by electrodessication, cryosurgery, Mohs micrographic surgery, and radiation therapy.

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Basal Cell Carcinoma with Matrical Differentiation

9

Sara C. Shalin and Bruce R. Smoller

Introduction

Basal cell carcinoma (BCC) is the most common type of skin cancer. Many variants are acknowledged, but the presence of matrical differentiation (recapitulating the follicular hair matrix) is exceedingly rare. Description of the entity is limited to single case reports or small case series.

Clinical Features

These tumors typically present in a manner similar to other BCC, with a predilection for sun-exposed sites. Usually the lesions arise as slowly growing nodules or plaques with occasional ulceration. Reported tumor sizes range from 0.5 to 10 cm in diameter. This subtype of basal cell carcinoma has once been reported arising in the setting of immunosuppression.

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Pathology

Most reported cases of this rare cutaneous tumor demonstrate at least focal areas of conventional basal cell carcinoma, characterized by islands and nests of basaloid cells with a high nuclear to cytoplasm ratio, peripheral palisading of tumor nuclei, clefting or retraction between tumor cells and the peritumoral stroma, and stromal mucin (Fig. 9.1). The presence of pilomatrix differentiation is recognized by the identification of shadow cells, which are epithelial cells with eosinophilic cytoplasm, preserved cell borders, and nuclear outlines, but complete loss of nuclear basophilia (Fig. 9.2). Shadow cells are thought to arise as a result of cell death following aberrant keratinization of hair follicles. Trichohyaline granules are sometimes apparent, supporting follicular derivation. The presence of calcification alone is not indicative of matrical differentiation.

Pilomatrical tumors (namely, pilomatricoma and pilomatrical carcinoma) have been described to have mutations in *CTNNB1* (the gene encoding β-catenin). A mutation in this gene has been variably detected (in 2 of 5 tumors tested) in basal cell carcinomas with matrical differentiation. Interestingly, the two tumors with mutations harbored the identical mutation in exon 3.

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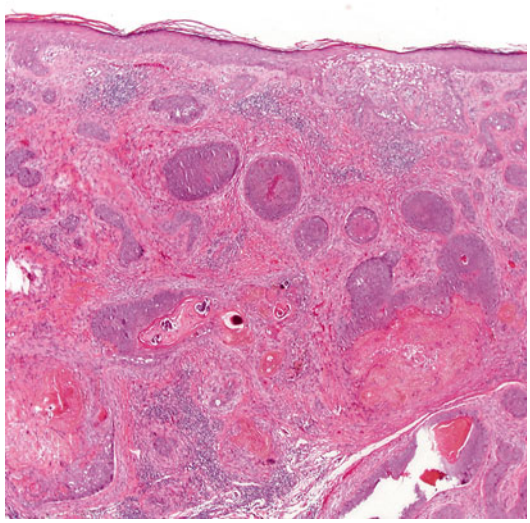

Fig. 9.1 Basal cell carcinoma with matrical differentiation. This punch biopsy demonstrates a basaloid tumor with epidermal connection. There is peripheral palisading of basaloid nests and focal tumor–stroma clefting. Islands of tumor demonstrate deeply eosinophilic "shadow cells"

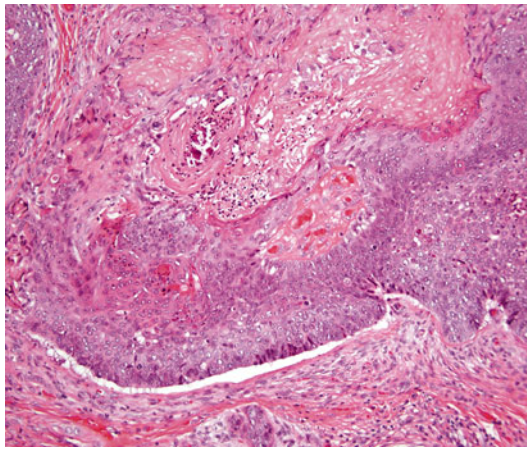

Fig. 9.2 Basal cell carcinoma with matrical differentiation. High magnification shows a nest of basal cell carcinoma that abruptly transitions to shadow cells. The shadow cells are characterized by eosinophilic cytoplasm, distinct cell borders, but no nuclear staining

Differential Diagnosis

Pilomatricoma (pilomatrixoma) is a benign adnexal tumor that recapitulates the hair matrix and demonstrates variable mixtures of basaloid and shadow cells, but is usually histologically distinct from basal cell carcinoma. Pilomatrical carcinoma (pilomatrix carcinoma) is the malignant counterpart of pilomatricoma and classically exhibits extreme cytologic pleomorphism, atypical mitotic figures, and an infiltrative border. It typically lacks the tumor–stroma retraction and nuclear palisading of tumor islands that is seen in basal cell carcinoma.

Both pilomatrical carcinoma and pilomatricoma have been shown to demonstrate diffuse and intense nuclear positivity for β-catenin. This is in opposition to the membranous and sometimes cytoplasmic pattern of immunoreactivity described in cases of basal cell carcinoma with matrical differentiation and the usual pattern of immunoreactivity in conventional nodular basal cell carcinomas.

Prognosis

Basal cell carcinoma with matrical differentiation appears to behave similarly to other basal cell carcinoma subtypes, although the rarity of the tumor type limits generalizations.

Treatment

Similar to other basal cell carcinomas, surgical excision (via Mohs micrographic surgery or conventional excision, depending on site) is the treatment of choice.

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Trichoblastic Carcinoma

10

Jennifer Kaley, Sara Shalin, and Bruce R. Smoller

Introduction

Trichoblastoma is a basaloid neoplasm recapitulating follicular differentiation with many variants and classifications in the literature. Its malignant counterpart, trichoblastic carcinoma, is a term interpreted differently depending on the authority queried. The term "trichoblastic carcinoma" refers to a malignant trichogenic adnexal tumor. Some authors broadly apply this designation to any malignancy with follicular germinative differentiation, and as such, entities including fibroepithelioma of Pinkus and basal cell carcinoma are considered conceptually to represent trichoblastic carcinomas (Ackerman et al. 2001; Ackerman and Gottlieb 2005; Sellheyer and Krahl 2008; Misago and AB 1999). Part of the argument in favor of this interpretation is the similar expression of adhesion molecules in developing follicles, the secondary hair germ, the outer root sheath, and basal cell carcinoma (Sellheyer and Krahl 2008), as well as identical cytokeratin expression profiles in fetal hair follicles, trichoblastoma, and basal cell carcinoma (Schirren et al. 1997).

However, this chapter intends to consider the diagnosis of trichoblastic carcinoma as a distinct entity representing the malignant transformation of trichoblastoma. This terminology is not recognized by all pathologists and thus is perhaps underdiagnosed (being more commonly termed basal cell carcinoma) (Triaridis et al. 2007; Laffay et al. 2012; Le Hemon et al. 2010). However, rare case reports are documented in the literature in support of the diagnosis of trichoblastic carcinoma as a distinct entity (Triaridis et al. 2007; Regauer et al. 2000; Rofagha et al. 2001; Schulz et al. 2005). These reports describe deeply infiltrative lesions, some resulting in systemic metastasis which would be exceptional in the case of basal cell carcinoma. Acknowledging that some amount of controversy exists regarding the nomenclature and classification of trichogenic neoplasms, in this section we will focus on the clinical and histological features that support the diagnosis of trichoblastic carcinoma as a distinct entity.

Clinical Features

Trichoblastic carcinoma usually presents on the scalp and face of middle-aged to elderly adults, affecting men and women equally (Rofagha et al. 2001). Lesions located on the forearm and thigh have also been reported (Schulz et al. 2005). The lesions are usually solitary, nodular, and greater than 1 cm in size.

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Pathology

Trichoblastic carcinomas typically demonstrate areas of pleomorphism and necrosis with adjacent background of otherwise typical trichoblastoma, which is characterized by small nests of follicular germinative cells with palisading peripheral nuclei and loose, fibrotic stroma recapitulating perifollicular sheaths. In contrast to benign trichoblastoma, the growth pattern becomes asymmetrical, deep, and infiltrative, with involvement of the fat or skeletal muscle (Figs. 10.1 and 10.2). Large basaloid nests lack the peripheral palisading and clefting between tumor and stroma as seen in basal cell carcinoma (Fig. 10.3). As in trichoblastoma, the lesion does not usually connect with the epidermis. Focal arrangement of squamous eosinophilic cells without keratinization may be seen and mitoses are conspicuous (Triaridis et al. 2007). When considering trichoblastic carcinoma as a diagnosis, lack of epidermal origin, cytologic atypia, conspicuous mitoses, absence of palisading, and absence of clefting are useful diagnostic features, although palisading and tumor-stroma clefting do not exclude the diagnosis (McKee et al. 2005) (Fig. 10.4).

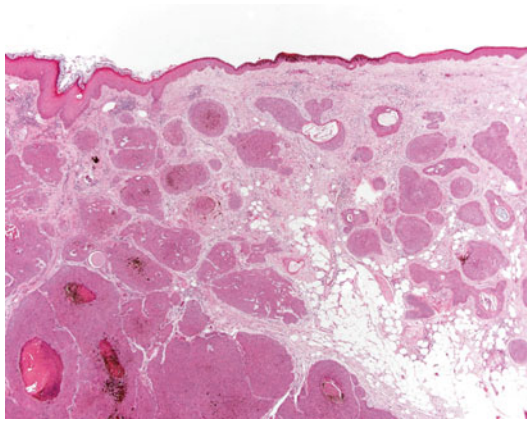

Fig. 10.1 Trichoblastic carcinoma. A large, asymmetrical lesion composed of basaloid islands with central comedo-type necrosis is adjacent to more typical-appearing trichoblastoma

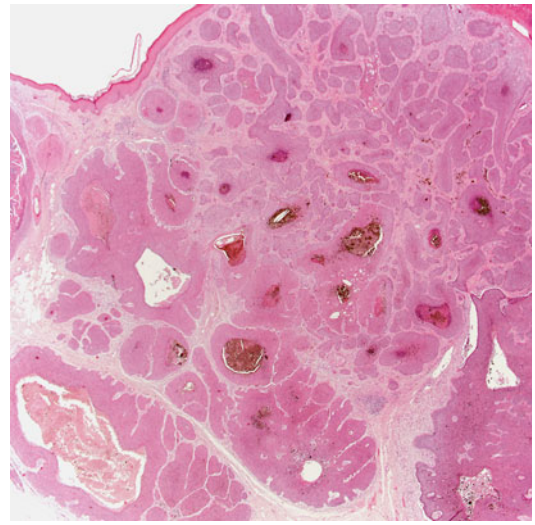

Fig. 10.2 Trichoblastic carcinoma. A deep, infiltrative, basaloid neoplasm is shown without well-developed connection to the epidermis

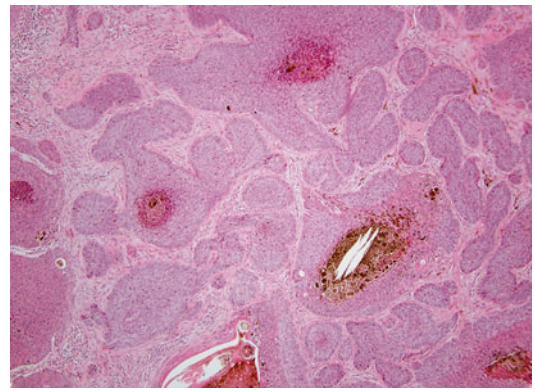

Fig. 10.3 Trichoblastic carcinoma. Basaloid tumor nests show with absence of tumor-stroma clefting, loose fibrotic stroma, and central necrosis

Differential Diagnosis

The diagnosis is primarily a histological one, but clinical features such as aggressive behavior can be helpful clues. The differential diagnosis includes basal cell carcinoma, trichoblastoma, trichilemmal carcinoma, and malignant pilomatricoma (Triaridis et al. 2007). The primary features that distinguish trichoblastic carcinoma from basal cell carcinoma are the lack of peripheral

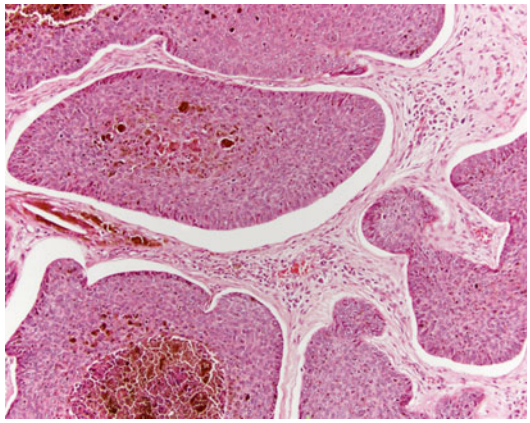

Fig. 10.4 Trichoblastic carcinoma. In some areas, epithelial islands show prominent peripheral palisading and tumor-stroma clefting, resembling basal cell carcinoma

palisading, lack of keratinization, nuclear pleomorphism, necrosis, and conspicuous mitoses seen in trichoblastic carcinoma. The presence of areas of benign appearing trichoblastoma merging with malignant areas is also a useful diagnostic clue. A benign trichoblastoma can be distinguished from its malignant counterpart by the lack of necrosis, cytologic atypia, and a brisk mitotic index. The neoplastic cells of trichilemmal carcinoma are clear and polygonal with peripheral palisading of cylindric cells. Malignant pilomatricoma typically demonstrate marked pleomorphism, an infiltrative growth pattern, and characteristic "ghost cells" due to aberrant keratinization (Triaridis et al. 2007).

Prognosis

Information regarding the prognosis of trichoblastic carcinoma is not readily available as the entity has been only rarely reported. Given the propensity to arise and expand deeply in the dermis, they may have a more aggressive course than basal cell carcinoma. As in other malignancies, the prognosis can be poor in the case of metastatic disease, especially in an immunocompromised patient. On the other hand, complete surgical excision can be curative.

Treatment

Complete surgical excision is the treatment of choice and is probably sufficient for the majority of tumors excised. Subsequent adjuvant radiotherapy may be useful in select cases demonstrating local aggressiveness (Laffay et al. 2012; Oufkir et al. 2013). A small study reported tyrosine kinase inhibitor therapy with sunitinib to be effective in patients with metastatic disease (Battistella et al. 2010).

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Malignant Proliferating Trichilemmal Tumor

11

Franco Rongioletti

Introduction

Malignant proliferating trichilemmal tumor (MPTT) is a dermal or subcutaneous neoplasm with squamoid cytologic features and trichilemmal-type keratinization. The term MPTT was entered in the literature in 1983 because of a proliferating trichilemmal tumor that showed infiltrative growth pattern, marked cytologic atypia, high mitotic activity, and lymph node metastases. However, proliferating trichilemmal cyst (tumor) was first recognized by Wilson-Jones in 1966 as an entity that had the histological capacity to simulate squamous cell carcinoma, although its malignant potential has not been stressed. Alternatively, some authors have proposed that proliferating trichilemmal cyst "should always be considered as a low-grade squamous cell carcinoma," and the term "proliferating follicular cystic SCC" has been proposed to encompass both conventional and malignant proliferating trichilemmal tumor. More than 30 cases of MPTT have been described in the literature, including 12 cases of metastatic disease, with several mortalities

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Clinical Features

MPTT is a rare skin tumor that affects the head and neck region of elderly women, mainly the scalp (Fig. 11.1). It most often arises in a proliferating trichilemmal cyst and typically undergoes a slow but progressive increase in size over several months to years, yielding lobulated and exophytic masses that occasionally ulcerate. The trigger for malignant changes is currently unknown, although trauma, inflammation, and irritation may play a role.

Pathology

The diagnosis of malignancy in these tumors is based predominantly on histological features. Multiple lobulated masses of squamoid epithelium filled centrally with homogeneous acellular eosinophilic material representing amorphous debris and pilar keratin are seen throughout all the dermis (Figs. 11.2 and 11.3) separated by fibrous or myxoid stroma. Areas of calcification are often present (Fig. 11.3). Trichilemmal keratinization (abrupt transition of a nucleated epithelial cell to an anucleate, keratinized cell without the formation of a granular layer) is a typical diagnostic clue. Foci of single cell necrosis and mitotic figures are present. In addition, the squamous cells may show slight cytologic atypia or manifest large, hyperchromatic nuclei with irregular nuclear membranes surrounded by abundant

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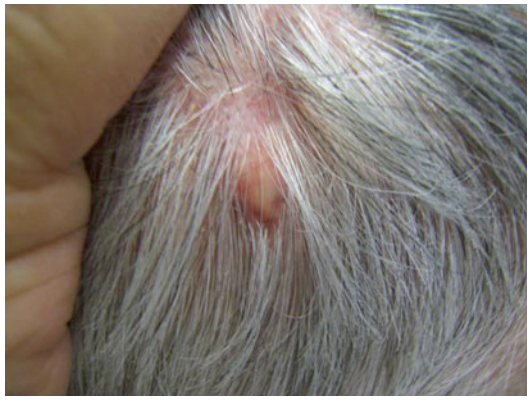

Fig. 11.1 Malignant proliferating trichilemmal tumor. A single hard, slow-growing nodular swelling 3×3 cm on the scalp. The lesion relapsed one year after excision

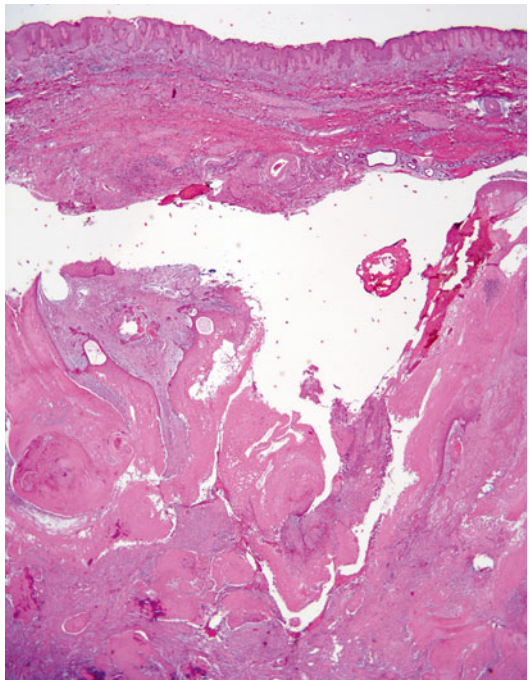

Fig. 11.2 Malignant proliferating trichilemmal tumor. Beneath the epidermis, multiple lobulated expansile masses of squamous cells with non-lamellated trichilemmal keratinization and patchy calcification are seen throughout the dermis and subcutis

eosinophilic cytoplasm with infiltrative pattern reminiscent of squamous cell carcinoma. A minimal to moderate infiltrate of mononuclear inflammatory cells was identified as well as foreign

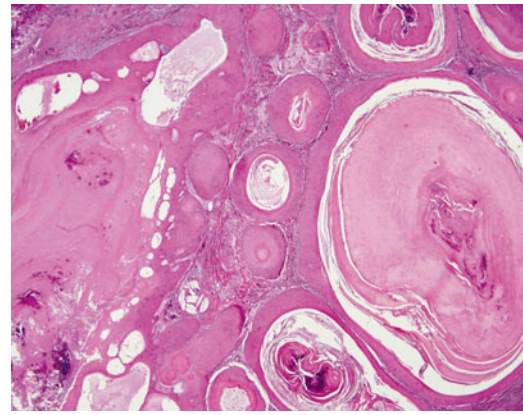

Fig. 11.3 Masses of squamoid epithelium with keratinous cysts filled centrally with homogeneous acellular eosinophilic material representing pilar keratin

body giant cell reaction to keratin. No lymphovascular or perineural invasion is noted. The tumor usually shows loss of staining for CD34, positivity for p53, high proliferative activity with Ki67, and DNA aneuploidy.

Differential Diagnosis

The main differential diagnosis is with squamous cell carcinoma. Features favoring the diagnosis of MPTT include the scalp location, the presence of trichilemmal-type keratinization, and the lack of a precursor epidermal lesion such an actinic keratosis. Trichilemmal carcinoma is different as it is a lobular proliferation centered around a follicle and composed of clear cells with basilar or full-thickness interfollicular epidermal spread in connection to the epidermis.

Prognosis

MPTT has greater malignant potential than histologically similar cutaneous squamous cell carcinoma, particularly tumors greater than 5 cm or with spindle cell components. Recurrences are not uncommon, and metastases have been reported in 30 % of cases as early as at the initial presentation and as late as 10 years.

Treatment

Wide local excision with a 1 cm margin is the appropriate treatment. More aggressive therapeutic measures such as nodal dissection, radiotherapy, or chemotherapy should be considered when wide local excision failed to cure the neoplasm or sometimes to prevent recurrences.

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Trichilemmal Carcinoma

12

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Introduction

Trichilemmal carcinoma (TC) is a rare cutaneous adnexal neoplasm that occurs on the sun-exposed areas of elderly people. The neoplasm was originally described as a clinical entity by Headington in 1976. The pathogenesis seems to be related to actinic damage, long-term low-dose irradiation, and malignant transformation of trichilemmoma.

Clinical Features

TC is characterized by erythematous, tan, or flesh-colored papules, nodules, or plaques that are frequently ulcerated. It occurs on sun-exposed areas, especially on the face (Fig. 12.1), scalp, neck, and back of the hands, mainly in elderly subjects but commonly between the fifth and ninth decades of life without any gender predilection. TC may arise in patients exposed to radiotherapy treatment with long latency periods or affected by xeroderma pigmentosum and in recipients of solid organ transplant. Presentation with multiple tumors and occurrence in Afro-American patients has been described. Spontaneous regression may occur, although it is extremely rare. Unlike trichilemmoma, TC is not associated with Cowden's syndrome.

Pathology

This neoplasm has been shown to exhibit outer root sheath differentiation and is considered to be a malignant form of trichilemmoma. A proliferation of lobular cells continuous with the epidermis, composed of large atypical cells with clear cytoplasm (Figs. 12.2 and 12.3) and PAS positivity, prominent nucleoli, frequent mitoses, and foci of trichilemmal keratinization, is the common pattern (Fig. 12.4). Rhodamine B stain highlights pilar keratin (Fig. 12.5). At the periphery of the lobules, the keratinocytes show palisading and are surrounded by a prominent connective tissue sheath. The tumor is purely intraepithelial, sometimes showing pagetoid spread or is more commonly associated with an invasive component centered around the pilosebaceous unit. Anecdotal cases of TC arising in seborrheic keratosis have been reported. The tumor cells are strongly positive for p53 and focally for CD 34 that is a marker of differentiation from the outer hair sheath. Moreover, TC expresses CK1, CK10, CK14, and CK17, suggesting that it differentiates toward follicular infundibulum. Neuroendocrine positivity with expression of chromogranin, synaptophysin, and CD56 is exceptional.

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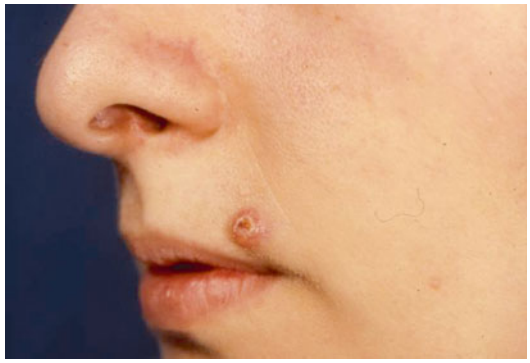

Fig. 12.1 Trichilemmal carcinoma. Flesh-colored nodule on the upper lip

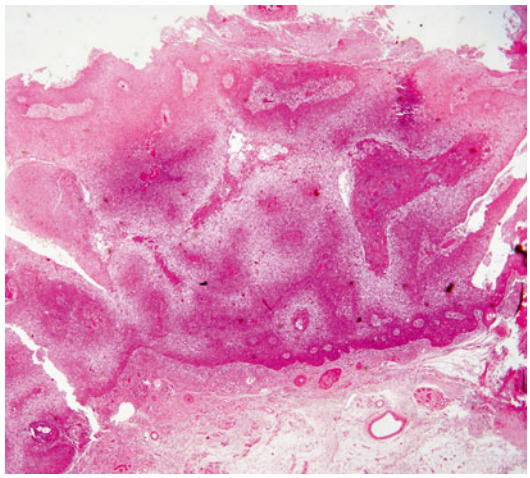

Fig. 12.2 A proliferation of lobular cells continuous with the epidermis, composed of large atypical cells with clear cytoplasm

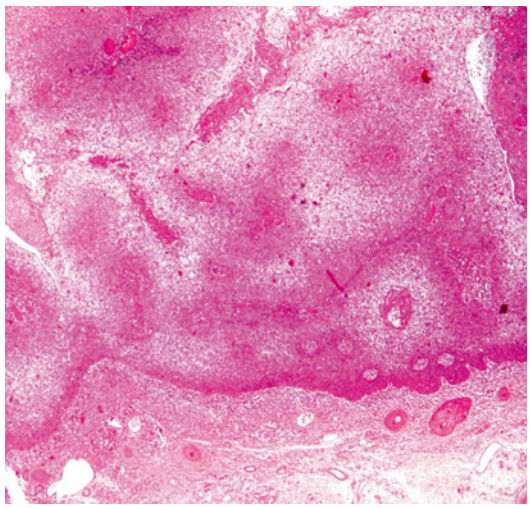

Fig. 12.3 Squamous islands with clear cells

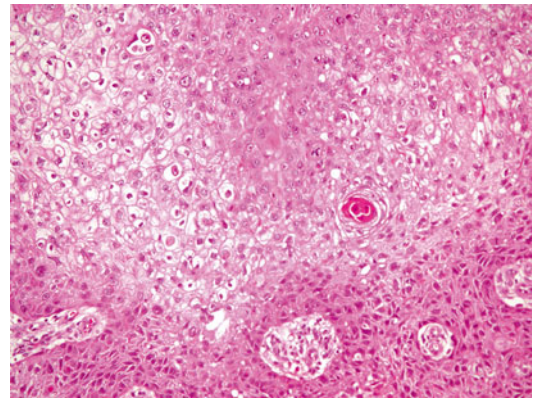

Fig. 12.4 Foci of trichilemmal keratinization with clear cells

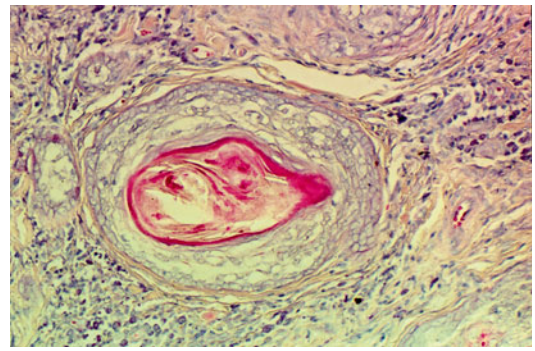

Fig. 12.5 Rhodamine B stain highlights pilar keratin

Differential Diagnosis

Malignant proliferating trichilemmal tumor is often confused with TC. Proliferating trichilemmal tumor usually arises in a preexisting trichilemmal cyst, is usually confined to the scalp, and is larger than TC (with a diameter of up to 20 cm). Histologically, proliferating trichilemmal tumor demonstrates sharply circumscribed lobules with pushing margins, deep dermal invasion, extensive areas of necrosis, abrupt keratinization, minimal pleomorphism, low mitotic activity, and foci resembling a trichilemmal cyst. TC must be differentiated from other skin cancers with clear cell changes. Squamous cell carcinoma lacks trichilemmal keratinization or lobular proliferation. Identification of ductal differentiation with CEA and EMA is useful for differentiating hidradenocarcinoma from TC. Desmoplastic benign trichilemmoma may exhibit an infiltrative growth pattern but lacks pleomorphism and mitoses.

Prognosis

It is considered a carcinoma of low malignancy with good prognosis for presenting low frequency of recurrences and rare metastases.

Treatment

The treatment is exclusively surgical with simple excision and adequate margins. However, 5 % imiquimod cream can be tried in difficult case.

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Pilomatrix Carcinoma

13

Irina Margaritescu and A. Doru Chirita

Introduction

Pilomatrix carcinoma (PC) or calcifying epitheliocarcinoma of Malherbe, originally described by Lopansri and Mihm in 1980, represents an exceedingly rare cutaneous neoplasm composed of aggregations of highly atypical basaloid cells and shadow cells that extend throughout the dermis and subcutaneous fat and have a propensity for local invasion, frequent recurrence, and distant metastasis.

Clinical Features

The tumor usually appears during the fifth decade of life, although it has been reported in young adults and even in children. Men are more commonly affected than women. The predilection sites are the head and neck areas, especially the scalp, the preauricular area, the posterior of the neck, and the back. Other reported sites are the upper extremities, buttocks, axilla, inguinal region, and the lower extremities. The tumor may present as a single, firm, non-tender, asymptomatic dermal, or subcutaneous tumor, or as a fungating, ulcerated mass (Fig. 13.1). Some tumors enter an accelerated growth phase after an initial stable or slow growing period. Others present as lesions with a few months duration and rapid growth. The tumor size ranges from 0.5 cm to 20 cm. It may be mistaken for a cyst, pilomatrixoma, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, or a sarcoma.

Pathology

The tumor is asymmetrical and poorly circumscribed and has a large size, usually extending throughout the dermis and subcutaneous fat (Fig. 13.2). The tumor usually has an infiltrating border. It can be locally aggressive with involvement of the fascia, skeletal muscle, and even bone. Some tumors demonstrate vascular, lymphatic, or perineural invasion. The lesion is composed of aggregates of neoplastic cells that vary greatly in shape and size and have jagged borders and a tendency for confluence. Extensive necrosis en masse is often present within these aggregations. Areas of dystrophic calcification can sometimes be present. The aggregates are composed of two populations of cells, namely, the basaloid cells and the "shadow" or "ghost" cells (Fig. 13.3). The basaloid cells usually predominate over the shadow cells (Fig. 13.4). The basaloid

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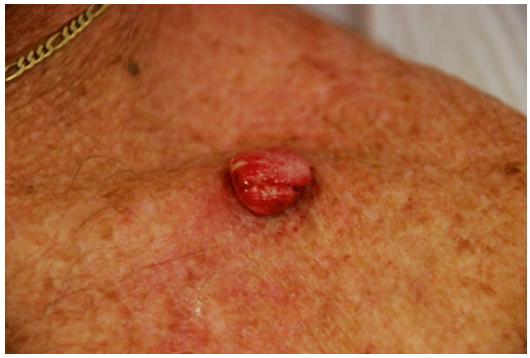

Fig. 13.1 Nodular ulcerated lesion on the left upper chest

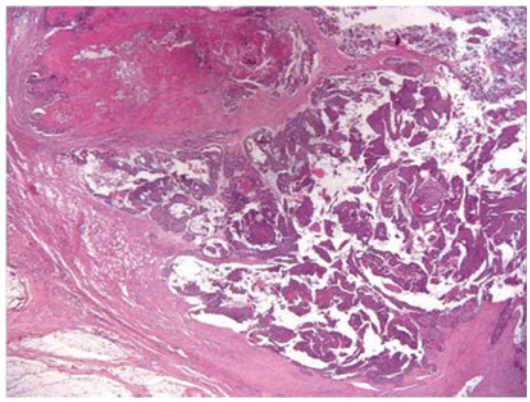

Fig. 13.2 This large epithelial neoplasm occupies the whole dermis and extends into the subcutaneous fat. It is composed of aggregations of neoplastic cells that vary in shape and size and have jagged borders

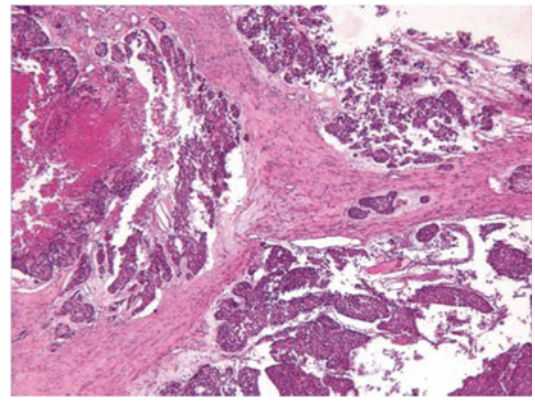

Fig. 13.3 The aggregations are composed of two populations of cells, namely, the basaloid cells and the "shadow" or "ghost" cells. Extensive necrosis en masse is present within some aggregations

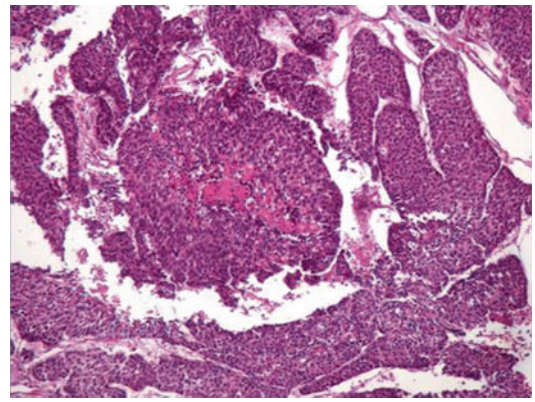

Fig. 13.4 The basaloid cells predominate over the shadow cells

cells are neoplastic, matrical cells that have pleomorphic and hyperchromatic nuclei and prominent nucleoli, scant cytoplasm, and numerous mitotic figures, including many atypical ones (Fig. 13.5). They give rise to the second population of shadow cells gradually or in a more abrupt fashion. The shadow cells have pale, eosinophilic cytoplasm and discrete ghost nuclei (Fig. 13.6). Sometimes, dendritic melanocytes can be seen between the basaloid cells and are responsible for the brown pigmentation of the tumor. The tumor is usually accompanied by a dense lymphoplasmacytic infiltrate. Granulomatous inflammation of foreign body type around foci of shadow cells can also be identified.

Differential Diagnosis

PC should be differentiated from other benign and malignant neoplasms with matrical differentiation such as pilomatricoma, proliferating pilomatricoma, aggressive pilomatricoma, mixed tumor, trichoepithelioma, and basal cell carcinoma (BCC) with matrical differentiation.

Pilomatricoma is a relatively symmetric, well-circumscribed, and mainly cystic neoplasm composed of uniform and small neoplastic basaloid cells arranged in bands or sheets at the periphery of aggregations of shadow cells. Although a predominance of basaloid cells with an increased number of mitotic figures can be seen in early

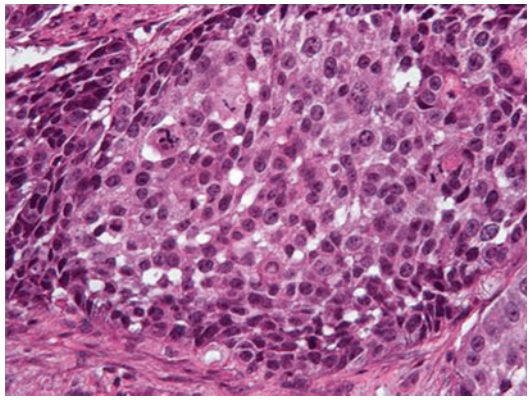

Fig. 13.5 The basaloid cells are neoplastic matrical cells that have pleomorphic and hyperchromatic nuclei and prominent nucleoli, and numerous mitotic figures, including atypical ones

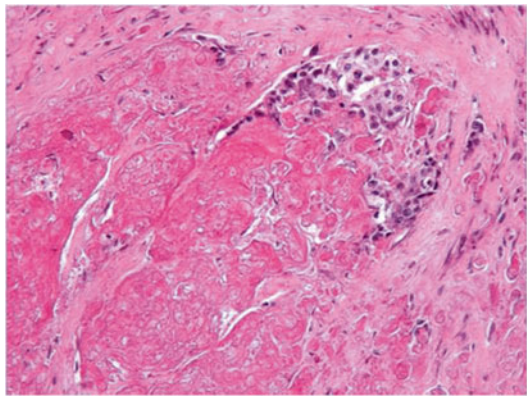

Fig. 13.6 The basaloid cells give rise to the second population of shadow cells with pale, eosinophilic cytoplasm and discrete ghost nuclei

evolving lesions, there is no pleomorphism or atypical mitotic figures. Moreover, no infiltrative pattern is evident in pilomatricoma.

Proliferating pilomatricoma is a relatively large lesion composed of a lobular proliferation of basaloid cells exhibiting variable nuclear atypia and an increased number of mitotic figures.

Aggressive pilomatricoma is composed of sheets of highly proliferating basaloid cells with mild cytologic atypia, prominent nucleoli, mitoses, and areas of necrosis. The tumor has an infiltrative growth pattern but is devoid of perineural or vascular invasion. Both proliferating and aggressive pilomatricoma have a propensity to recur locally, but no lymph node involvement or distant metastasis has been recorded so far.

BCC with matrical differentiation shows typical areas of germinative cells arranged in aggregations with a peripheral palisade and an artifactual cleft between these aggregations and the adjacent stroma.

PC should also be differentiated from squamous cell carcinoma, proliferating pilar tumor, sebaceous carcinoma, and lymphoepithelial-like carcinoma. Although these neoplasms share some morphological characteristics with PC, each of them can be differentiated from PC by their distinctive histological features and absence of matrical differentiation.

Finally, PC should be differentiating from the exceedingly rare cutaneous metastasis of poorly differentiated visceral carcinoma with shadow cell differentiation.

Prognosis

PC is a locally aggressive neoplasm with a great propensity for local recurrence unless excised with wide margins. About 10 % of the cases reported in the literature have metastasized especially in the lungs, lymph nodes, and bones. Widespread metastases have also been reported.

Treatment

Complete surgical excision of the tumor with wide margins is the treatment of choice. Other treatment options include Mohs micrographic surgery and adjuvant radiation therapy.

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Sebaceous Gland Carcinoma

14

Franco Rongioletti

Introduction

Sebaceous carcinoma (SC) is an aggressive, malignant tumor derived from the adnexal epithelium of sebaceous glands that can occur in ocular/periocular (75 % of all SC) and extraocular variants. Its incidence varies according to the ethnicity. In Caucasians, SC accounts for 1–5.5 % of eyelid malignancies, while in Asiatic people, it is the second most common eyelid malignancy after basal cell carcinoma with an incidence of 38 %. Ocular SC occurs more frequently in women (3:1), while the extraocular form has a predilection for men (2:1). The age of presentation varies from 60 to 80 years. SC may occur in the setting of Muir–Torre syndrome, after radiotherapy or in immunocompromised patients such as HIV-infected patients.

Clinical Features

Periocular SC arises in the Meibomian glands of tarsus, in the Zeis glands, and in the sebaceous glands of caruncle or eyebrow and is three times more frequent on the upper eyelid. A slow-growing, painless pinkish or red nodule commonly located in the upper or lower tarsal plate is a common presentation (Fig. 14.1). Sometimes, a yellowish appearance is a clue for clinical suspicion. The pagetoid variety occurs as a mass of firm consistency with intraepithelial infiltration of the lid margin and/or conjunctiva, causing diffuse thickening and loss of eyelashes. In one third of the cases, there is a tendency for ulceration and spontaneous bleeding. The clinical findings may mimic an inflammatory disease such a chalazion or blepharitis, causing a delay in diagnosis by 1–2.9 years. SC may be multicentric with the simultaneous occurrence at noncontiguous sites that in ocular tumors constitutes involvement of the upper and lower eyelids. The extraocular SC derives from the sebaceous glands of the hair follicles. The most frequent localization of the extraocular SC is the head and neck (Fig. 14.2). A giant extraocular form has been reported.

SC can present as an isolated lesion or a part of the Muir–Torre syndrome, a rare autosomal-dominant genodermatologic disorder characterized by sebaceous gland tumors, nonpolyposis colorectal carcinoma, and visceral malignancies (endometrial, urological) (Fig. 14.3). Approximately 23 % of the patients with Muir–Torre syndrome have sebaceous carcinoma. Muir–Torre syndrome is due to defective DNA mismatch repair (MMR) genes. The MMR proteins mainly related to Muir–Torre syndrome are MSH2 (on chromosome 2), MLH1 (on chromosome 3), and MSH6 (on chromosome 2).

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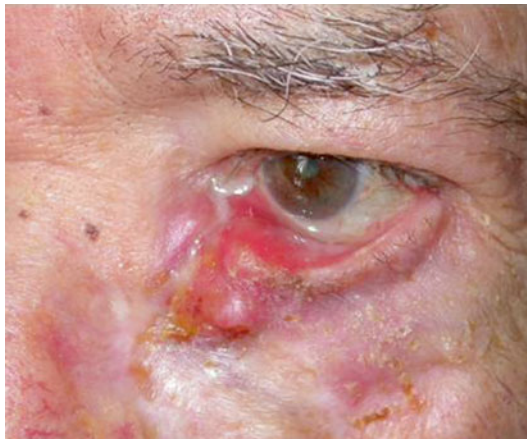

Fig. 14.1 Sebaceous carcinoma. A slow-growing, painless pinkish nodule on lower tarsal plate

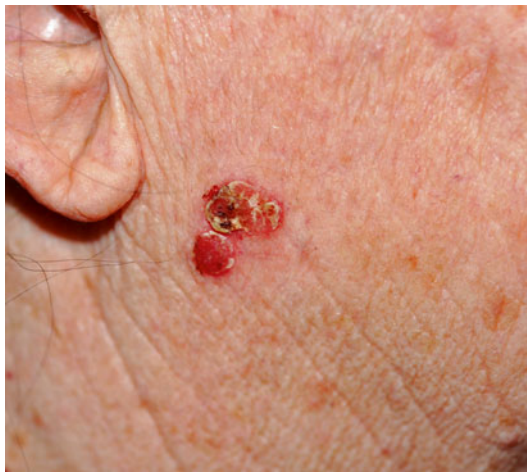

Fig. 14.2 Sebaceous carcinoma. An erythematous slowly enlarging nodular plaque with a yellowish hue on the face

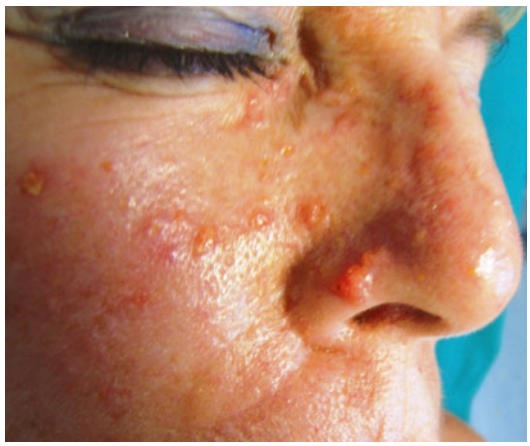

Fig. 14.3 Muir–Torre syndrome. Sebaceous carcinoma on the nose with multiple sebaceous adenomas

Pathology

SC may be classified as well, moderately, or poorly differentiated. The most common presentation is characterized by irregular lobules and sheets with distinctive invasiveness containing cells whose cytoplasm is pale, foamy, and multivacuolated (Figs. 14.4 and 14.5). Some atypical eosinophilic-keratinizing cells with keratin pearls, as seen in squamous cell carcinoma, are found in larger lobules (Fig. 14.6). SC commonly shows considerable nuclear and nucleolar pleomorphism, abnormal mitoses, and zones of central necrosis. In the poorly differentiate variant, basaloid cells are predominant with only a small minority of recognizable sebocytes (Fig. 14.7). Regardless of grade, intraepithelial

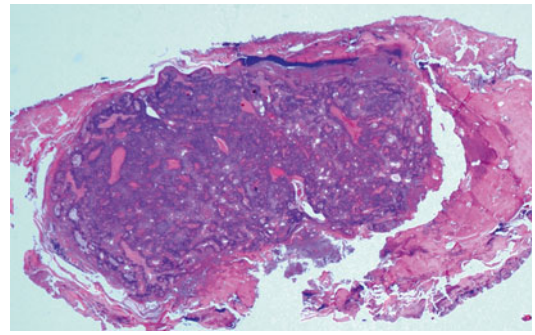

Fig. 14.4 A basaloid dermal-based nodular proliferation of irregular lobules and sheets

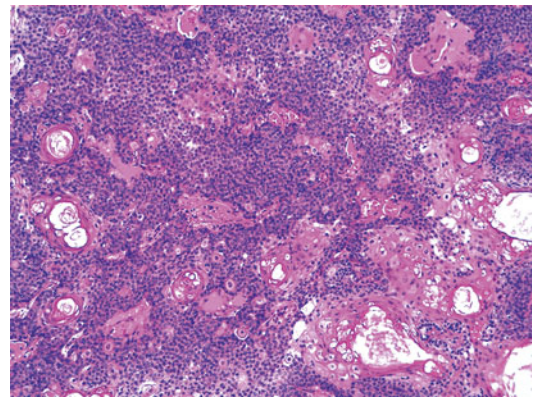

Fig. 14.5 Neoplastic cells with basaloid appearance and eosinophilic cells with lipid globules. Some atypical eosinophilic-keratinizing cells with keratin pearls are visible

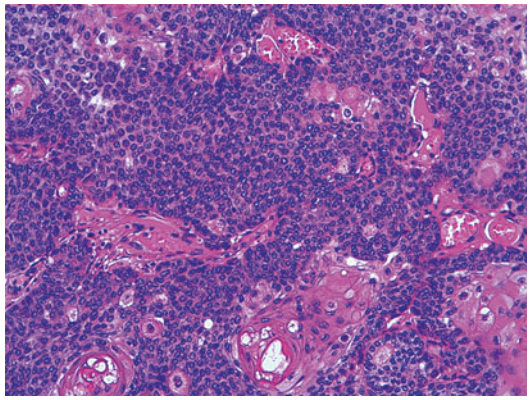

Fig. 14.6 A basaloid area with scattered vacuolated clear cells showing sebaceous differentiation and keratinizing cells

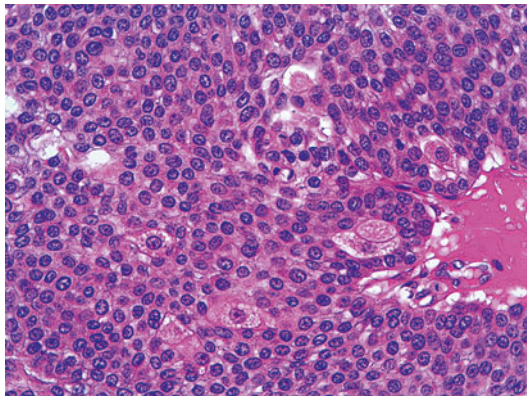

Fig. 14.7 Some atypical multivacuolated cells with sebaceous differentiation and scattered mitotic figures

pagetoid spread and/or multicentric pattern are often seen.

SC is positive for EMA, Ber-EP4, androgen receptor, cytokeratin 7, CAM 5.2, and BRST-1. The tumor is negative for CEA, S100 protein, or gross cystic disease fluid protein-15. Androgen receptor appears to be more sensitive than EMA in poorly differentiated SC. However, 60 % of basal cell carcinoma may also show focal expression of androgen receptor.

Adipophilin, perilipin, and TIP47 stains that can be performed on formalin-fixed paraffin-embedded tissue are useful for recognizing proteins present on the surface of intracellular lipid droplets.

The immunohistochemical analysis should include MLH1, MSH2, MSH6, and PMS2. A lack of nuclear immunoreactivity within tumor cells is supportive of a mutation in the tested gene and has been shown to correlate with high levels of Muir–Torre syndrome.

Differential Diagnosis

Ocular SC may mimic chronic inflammation such as chalazion and blepharoconjunctivitis. Histologically, the main differential diagnosis is with malignant clear cell skin tumors such as clear cell squamous carcinoma, trichilemmal carcinoma, clear cell eccrine carcinoma, and metastatic clear cell carcinomas of visceral origin. Valuable *clues* to *the diagnosis* of SC are the findings of clusters of sebaceous cells and small *duct*-like *structures* lined by eosinophilic *cuticles.* Basal cell carcinoma with sebaceous differentiation and squamous cell carcinoma should be differentiated from basaloid or squamoid SC that carries a less favorable prognosis. An EMA-positive, Ber-EP4-positive immunophenotype supports SC.

Prognosis

Eyelid SC is characterized by a high recurrence rate, a tendency for intraepithelial pagetoid spread and for locoregional and distant metastases. For years, the extraocular tumors were thought to have a worse prognosis. Actually, the biological behavior and prognosis of SC are no more considered to depend on the site of involvement. The main prognostic factor is the time to diagnosis; when the diagnosis is made in the first six months, the mortality rate is about 14 %. After the sixth month, the mortality rates rise to 38 %. Decreased p27 expression has been reported as a predictive marker of an unfavorable course.

Treatment

The first-line treatment is surgical excision with wide margins (at least of 5–10 mm). SC has a local recurrence that varies from 9 to 36 % in 5 years after surgical excision. Nodal metastasis occurs in

approximately 8–28 % of cases. Mohs surgery appears to be a good alternative therapeutic option with lower local recurrence rates (approximately 12 %). Sentinel node biopsy has been used in both ocular and extraocular sebaceous carcinomas, but it is not a standard technique and its clinical utility has yet to be confirmed. Radiotherapy may have a role in the treatment of metastatic sebaceous carcinoma, in patients with orbital involvement who refuse excision, and in elderly patients with local recurrence. Efficacy of capecitabine has been reported in an anecdotal metastatic case.

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Part III

Tumours of Apocrine Gland

Primary Cutaneous Apocrine Adenocarcinoma

15

Irina Margaritescu and A. Doru Chirita

Introduction

Primary cutaneous apocrine adenocarcinoma first described by Horn in 1944 represents a very rare tumor with less than 100 cases reported in the literature.

Clinical Features

The tumor usually appears in the areas rich in apocrine glands or modified apocrine glands such as ceruminous and Moll's glands. The axilla is the most common site affected (approximately in 60 % of all cases), followed by the anogenital area, scalp, chest, nipple, eyelid, and ear. Other reported sites are the arm (near axilla), cheek, wrist, foot, toe, fingertip, submandibular area, and lip. The age at presentation ranges from 18 to 91 years, with an average age of 60 years. Males and females are equally affected, and there is no racial predilection. The usual presentation is a single painless slowly growing nodule or plaque with an erythematous or purplish hue of the overlying tegument (Fig. 15.1). Sometimes, it may present as an indurated or morpheaform plaque, as papulovesicles in a band-like arrangement, or as an ulcerated mass. It may appear de novo or develop within a preexisting benign lesion such as an apocrine hyperplasia, apocrine adenoma, cylindroma, spiradenoma, and syringocystadenoma papilliferum or in a nevus sebaceous. Because of their indolent course, most apocrine carcinomas are diagnosed after many years, when they usually reach 1–3 cm in diameter. Tumors as large as 8 cm in diameter have been described. Approximately half of these neoplasms have lymph node metastases at the time of diagnosis. Apocrine carcinoma may be mistaken for ectopic breast tissue, benign apocrine neoplasm, lymphoma, metastatic breast carcinoma, squamous cell carcinoma, or colorectal adenocarcinoma.

Pathology

Primary cutaneous apocrine adenocarcinoma is an asymmetrical, poorly demarcated neoplasm with an infiltrating border, situated in the reticular dermis and subcutaneous tissue. Sometimes, the tumor extends into the epidermis in the form of franc extramammary Paget's disease

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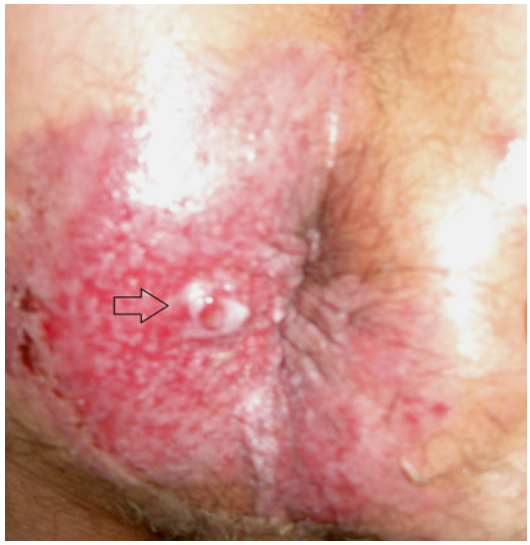

Fig. 15.1 This 63-year-old man presented with a slow-growing indurated nodule in association with a long-standing ill-defined erosive erythematous plaque in the perianal region

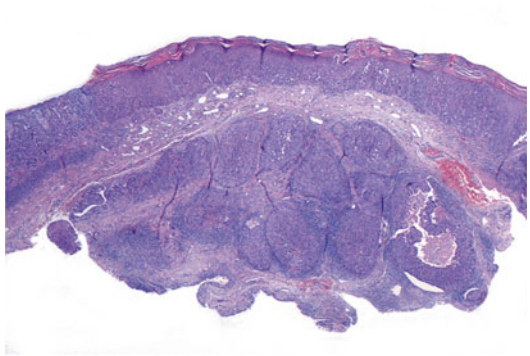

Fig. 15.2 The biopsy of the nodule shown in Fig. 15.1 displays a poorly differentiated apocrine adenocarcinoma with a solid growth pattern located in the reticular dermis. The tumor extends into the epidermis in the form of franc extramammary Paget's disease

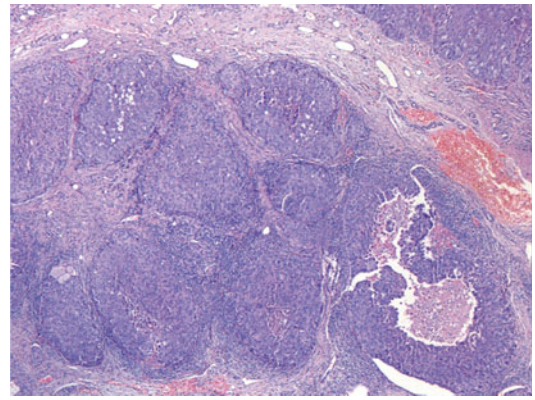

Fig. 15.3 The solid aggregations vary in size and shape and exhibit tumoral necrosis

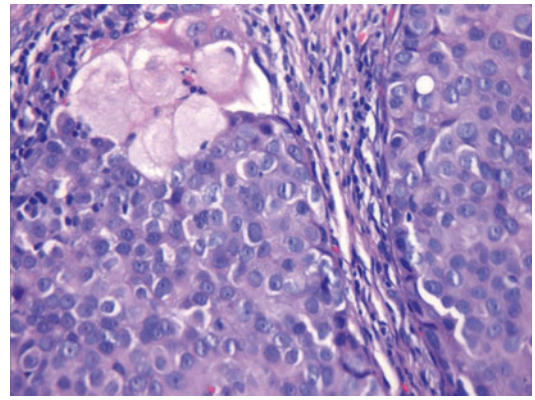

Fig. 15.4 The neoplastic cells have round or oval vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. Some cells demonstrate mucin-laden cytoplasm. Focally, the neoplasm shows ductal differentiation

(Fig. 15.2). The neoplasm grows in different patterns including tubular, papillary, tubulopapillary, cystic, cribriform, diffuse, or solid growth pattern (Fig. 15.3). An "Indian file" growth pattern can also be encountered. The tumor is commonly accompanied by a dense hyaline stroma. Signs of apocrine differentiation such as decapitation secretion and papillary projections into the lumina are almost invariable present. However, these signs maybe lacking in poorly differentiating carcinoma. Areas of tumor necrosis can also be encountered. The neoplastic cells have round or oval vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm (Fig. 15.4). Signet-ring cell features are sometimes encountered, especially in eyelid tumors

with a striking predominance in elderly males. There is a variable cellular pleomorphism and an increased mitotic activity, especially in poorly differentiated neoplasms.

Histochemistry

Diastase-resistant, PAS-positive, and iron-positive intracytoplasmic granules are characteristically seen in apocrine carcinoma. Apocrine differentiation markers alpha-1-antitrypsin and lysozyme are commonly expressed by the tumor cells. Also, Alcian blue and mucicarmine stains are sometimes positive.

Immunohistochemistry

The tumor cells of primary cutaneous apocrine carcinoma usually express CK5/6, CEA, EMA, AR, and GCDFP-15 (Fig. 15.5a–f) and are negative for bcl-2, Her2neu, and c-erbB-2. The cells stain variably with p63, ER, and PR. Mammaglobin and D2-40 are either negative or positive in scattered cells.

Differential Diagnosis

Primary cutaneous apocrine adenocarcinoma should be differentiated from other benign and malignant neoplasms with apocrine differentiation, especially from apocrine adenoma, metastatic breast apocrine carcinoma and apocrine carcinoma arising in ectopic breast tissue, and mucinous carcinoma. Depending on location, cutaneous apocrine carcinoma should also be differentiated from metastatic colorectal adenocarcinoma and metastatic adenocarcinoma of the genitourinary tract. In differentiating primary from metastatic apocrine carcinoma, immunohistochemistry is just an adjunctive tool, and it cannot replace a careful and detailed history coupled with a thorough clinical examination and imaging studies.

Prognosis

Usually, apocrine carcinomas have an indolent course and may achieve long-term remission only with surgical treatment. Lymph node metastases are found in up to half of the patients at the time of diagnosis. Moderately and poorly differentiated tumors have a higher propensity for local recurrence and distant metastases.

Treatment

Wide surgical excision of the tumor with sentinel lymph node biopsy is the standard treatment for apocrine adenocarcinoma. Mohs micrographic surgery could be the treatment of choice for those carcinomas situated in functionally or cosmetically limiting locations (eyelid, fingertip, lip). Adjuvant radiotherapy and chemotherapy have not proven to be beneficial in patients with moderately or poorly differentiated neoplasms.

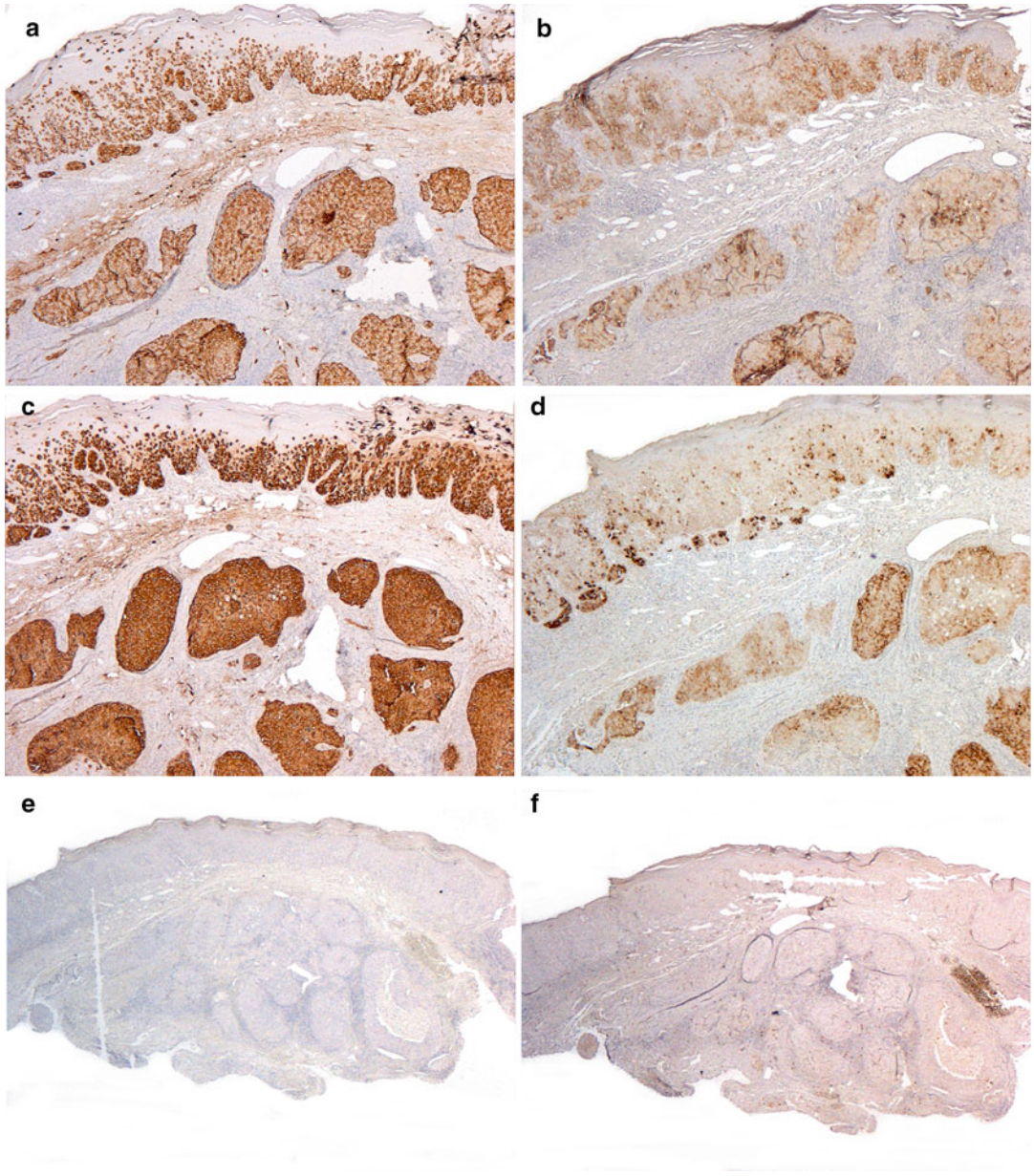

Fig. 15.5 Immunohistochemically, the dermal tumoral cells share an identical profile with the neoplastic cells in the overlying epidermis. They are positive for (**a**) CK7, (**b**) CEA, (**c**) EMA, and (**d**) GCDFP-15 and negative for (**e**) CK20 and (**f**) S100

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Extramammary Paget's Disease

16

Irina Margaritescu and A. Doru Chirita

Introduction

Extramammary Paget's disease, originally described by Crocker in 1889, is a rare apocrine adenocarcinoma that appears in the epidermis and from there may extend into the epithelial structures of adnexa and dermis. The pathogenesis of EMPD is still controversial. There are two different forms of EMPD with distinct pathogenetic mechanisms. The "primary" form represents the majority of the cases and is considered the only true EMPD. It originates in the skin, presumably from an undifferentiated pluripotent cell of the epidermis and/or its adnexa. It has also been suggested that Toker cells, an intraepidermal cell with abundant clear to pale cytoplasm present in the nipple, along the milk line and in the vulva, are the benign precursors of Paget cells. The "secondary" EMPD form constitutes about 25 % of cases and is considered to represent an epidermotropic spread from an underlying adnexal or visceral adenocarcinoma (genitourinary, gastrointestinal, or another distant site).

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Clinical Features

EMPD typically appears in the middle-aged to elderly people (range 45–85 years). It is seen more frequently in women, with a female-to-male ratio of 4:1, except for Japan and Korea where there is a male predominance. The most common location is the vulvar region, which accounts for almost half of all cases, followed by the perineum, perianal region, scrotum, and penis. Less commonly, it can appear on any skin or mucosal area rich in apocrine glands such as the axilla, buttocks, thighs, eyelids, and external auditory canal. Other affected sites are the chest, arms, fingers, knees, back, and cheeks (so-called ectopic EMPD). EMPD may occur simultaneously in the anogenital and axillary region. Concurrent mammary and extramammary disease also exists. Cases of triple and even quadruple EMPD have been published, mostly in the Japanese literature. Typically, the lesions of EMPD present as slowly enlarging, well-demarcated, erythematous, eczematous, or leucoplakic plaques, measuring one or several centimeters in diameter (range 1–15 cm) (Fig. 16.1). The lesions may become erosive, ulcerated, infiltrated, or vegetating. Hard nodules and regional lymph node enlargement may develop in time. Pruritus is the most common accompanying symptom. Other symptoms such as burning, pain, or tenderness may be present, although a small proportion of cases can

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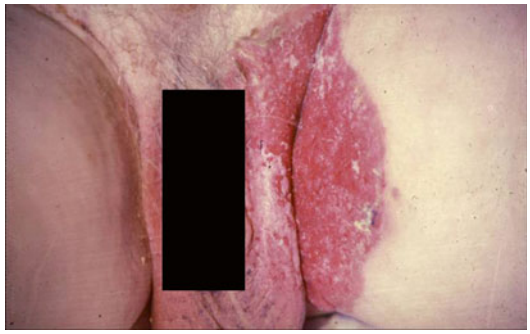

Fig. 16.1 Slowly enlarging, well demarcated, erythematous, eczematous plaque in the left inguinal area and on the scrotum

be asymptomatic. Due to its subtle onset and nonspecific clinical features, an accurate diagnosis is often delayed (by 4 months to 15 years). The main clinical differential diagnosis of EMPD includes eczema, contact dermatitis, fungal infection, psoriasis, lichen sclerosus, Bowen's disease, superficial basal cell carcinoma, and mycosis fungoides.

Pathology

EMPD is an asymmetrical, multicentric, poorly demarcated neoplasm in which the atypical epithelial cells are disposed within the epidermis and epithelial structures of adnexa. The cells are arranged as solitary units and in nests of different sizes in the basal layer, throughout the epidermis, and within the depth of epithelial structures of eccrine ducts and folliculosebaceous units (Fig. 16.2). Nests of Paget cells are not equidistant from one another and have a tendency to confluence and to form glandular structures. Most cells are concentrated in the lower portion of the epidermis and in the epithelial structures of adnexa. The neoplastic cells have round or oval pleomorphic nuclei, prominent nucleoli, and abundant pale cytoplasm with a bluish cast due to intracytoplasmic mucin. This may not always be apparent on routine sections. Occasionally, Paget's cells can take on a signet-ring appearance due to intracytoplasmic accumulation of mucin (Fig. 16.3). Signs of apocrine differentiation in the form of glandular formation with decapitation secretion and mucinous cells are sometimes seen (Fig. 16.4). An underlying adnexal adenocarcinoma may occasionally be found.

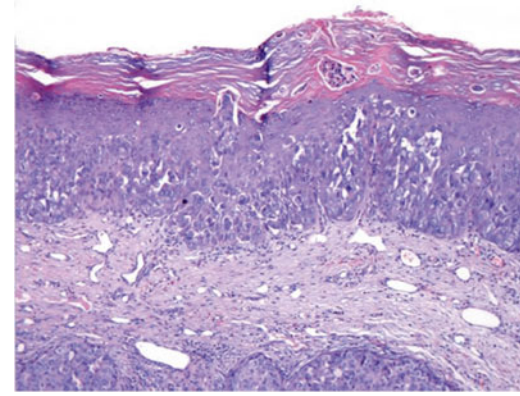

Fig. 16.2 The atypical epithelial cells are disposed as solitary units and in nests throughout the epidermis, mostly in the lower portion of it

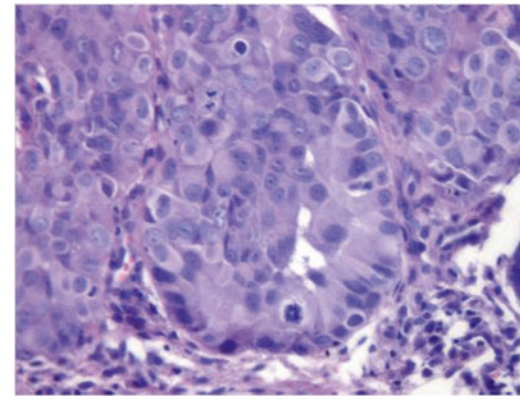

Fig. 16.3 The neoplastic cells have round or oval pleomorphic nuclei, prominent nucleoli, and abundant pale cytoplasm with a bluish cast. Occasionally, the cells take on a signet-ring appearance due to intracytoplasmic accumulation of mucin

Histochemistry

Paget cells are diastase-resistant, PAS-positive, Alcian blue-positive, mucicarmine-positive,

aldehyde fuchsin-positive, and toluidine blue-positive cells. Apocrine differentiation markers α-1-antitrypsin and lysozyme are commonly expressed by the tumor cells.

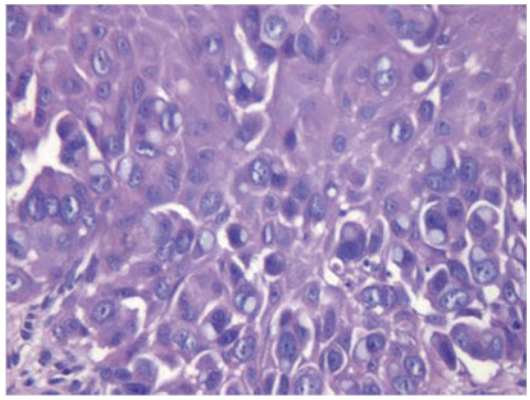

Fig. 16.4 Glandular formation with hints of decapitation secretion is also seen. Many mitotic figures, including atypical forms, are easily identified

Immunohistochemistry

The tumor cells of EMPD usually express CK5/6, CK7, CEA, EMA, AR, Her2neu, and GCDFP-15 (Fig. 16.5a–d) and are negative for ER, PR, bcl-2, and c-erbB-2. CK20 is usually negative in primary cutaneous EMPD and positive in secondary EMPD. CDX2 for colon, PSA for prostate, and uroplakin for bladder carcinoma are useful markers in the evaluation of EMPD with an underlying tumor.

Differential Diagnosis

Differential diagnosis of EMPD includes entities in which the cells are distributed singly or in small groups throughout the epidermis. Pagetoid dyskeratosis is characterized by large, round keratinocytes with pale cytoplasm that may resemble

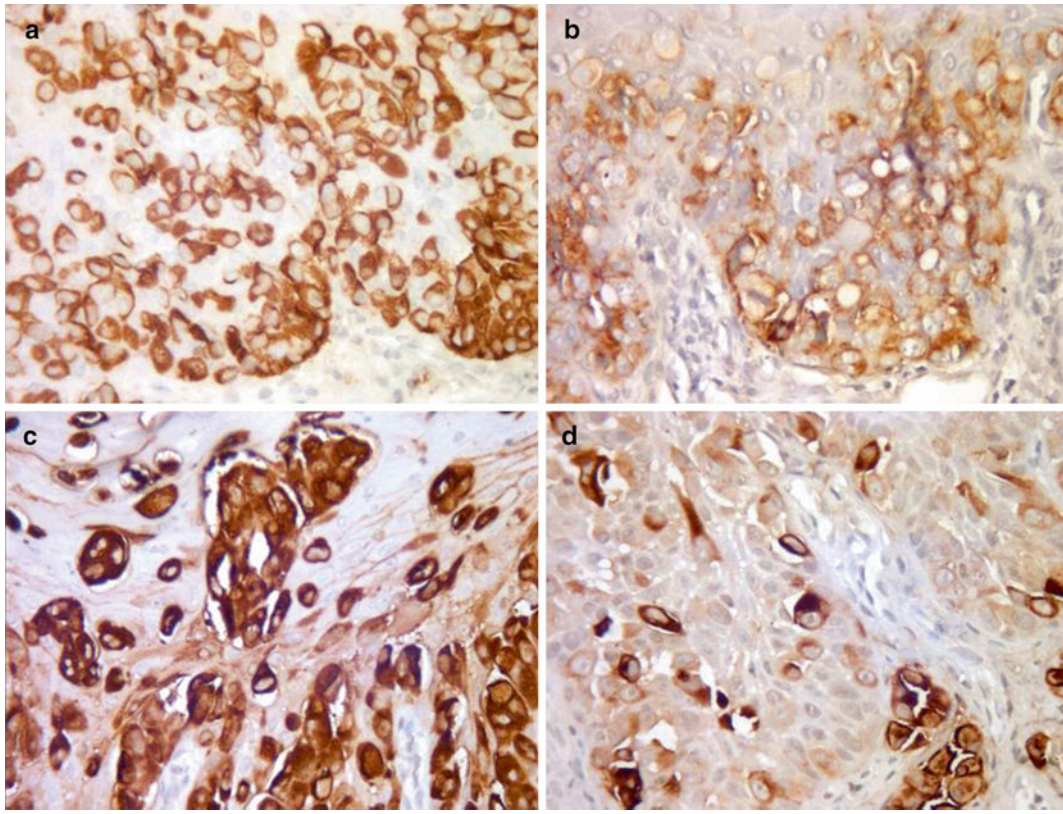

Fig. 16.5 The tumor cells characteristically express (**a**) CK7, (**b**) CEA, (**c**) EMA, and (**d**) GCDFP-15

Paget cells. However, the cells in pagetoid dyskeratosis have pycnotic nuclei surrounded by a clear halo and are disposed predominantly in the granular and upper malpighian layer. Moreover, these cells usually express high molecular weight keratins, but not low molecular weight keratins (such as CK7), EMA, or CEA. The appearance and distribution of Toker cells in Toker cell hyperplasia may lead to confusion with EMPD. In contrast to the pleomorphic cells with atypical nuclei of EMPD, however, Toker cells are smaller and display small, uniform, and eccentric nuclei. Clear cell papulosis can resemble EMPD as it shows solitary enlarged pale cells disposed in the basal layer and sometimes in the malpighian layer as well. Unlike Paget cells, however, the cells in clear cell papulosis do not form nests or tubular structures. Moreover, clear cell papulosis is characterized clinically by multiple small, whitish maculopapules distributed along the milk line in children of Asian descent. Distinction between EMPD and pagetoid Bowen's disease can prove difficult. Both of them show cells with round nuclei and abundant pale cytoplasm arranged as solitary units and in aggregations at all levels of the epithelium. The features that point towards EMPD are the presence of intracellular mucin and glandular structures and the absence of intercellular bridges and signs of cornification. A panel of immunohistochemical stains which include CK7, CAM 5.2, EMA, CEA, GCDFP-15, and p63 aids in differential diagnosis. Distinguishing EMPD, especially the pigmented variant, from melanoma is also difficult. However, the atypical cells in melanoma are situated predominantly at the dermoepidermal junction, whereas the Paget cells of EMPD are disposed in the basal layer and above it, in a more diffuse fashion. Moreover, intracellular mucin and acinar formation are not features encountered in melanoma. Ultimately, immunohistochemical stains may be used to differentiate these entities. The distribution of neoplastic lymphocytes in pagetoid reticulosis may simulate the distribution of Paget cells in EMPD. However, the atypical lymphocytes have characteristic convoluted nuclei and less abundant cytoplasm. Immunohistochemical stains readily distinguish between the two. Histiocytosis X can be distinguished from EMPD by its characteristic cytologic features and immunohistochemistry. When it presents as an intraepidermal carcinoma, sebaceous carcinoma may resemble EMPD. However, in sebaceous carcinoma, the cells have a vacuolated appearance with cytoplasmic microvesiculation as opposed to the basophilic appearance of Paget cells.

Prognosis

The biological course of primary EMPD is usually benign. In most cases, the disease remains confined to the epidermis and epithelial adnexa for years. Although rare, invasion of the underlying dermis, blood, and lymphatic vessels by the tumor cells can occur and portends a worse prognosis. The prognosis of secondary EMPD depends on the prognosis of the underlying carcinoma.

Treatment

There is no standard treatment for EMPD. Mohs micrographic surgery is the first-line treatment for EMPD. However, there is a high recurrence rate, due to the multifocal nature of the disease and the presence of clinically occult extensions. Topical imiquimod, topical 5-fluorouracil (5-FU), and retinoic acid, alone or in combination, proved to be beneficial in some cases. Other treatment modalities may include CO2 laser ablation, photodynamic therapy, and adjuvant radiotherapy.

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Primary Cutaneous Adenoid Cystic Carcinoma

17

Sara C. Shalin and Bruce R. Smoller

Introduction

Primary cutaneous adenoid cystic carcinoma is a rare adnexal neoplasm. Both eccrine and apocrine glands have been posited to be the source of this tumor; however, its precise histogenesis remains unclear. It bears considerable histological and immunophenotypic similarity to its salivary gland counterpart but behaves in a less aggressive manner.

Clinical Features

Primary cutaneous adenoid cystic carcinoma arises most frequently as a slow-growing nodule or indurated plaque on older individuals, although the tumor has been reported in a wide range of ages. Some studies document a male predilection, while others report an approximately equal incidence in males and females, and yet others indicate a female preponderance. Although the head and neck region (particularly the scalp) represents the most common location, this neoplasm can occur at other body sites, including the vulva, where it may display more aggressive behavior and a higher propensity for metastasis.

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Pathology

A systematic study of cutaneous adenoid cystic carcinoma by Seab and colleagues proposed a minimal set of histological criteria for diagnosis, including a dermal-based tumor composed of basaloid tumor cells set in a basophilic mucinous stroma and demonstrating at least a focal cribriform pattern. Epidermal involvement is unusual, and the poorly circumscribed tumors are typically based in the dermis with frequent extension to the subcutis. The tumor is comprised of columns, nests, and islands of relatively monotonous cells arranged concentrically around pseudocystic spaces filled with basophilic or eosinophilic material (Fig. 17.1). Basement membrane material may be present on the intraluminal aspect of the cystic spaces and can be a helpful clue to diagnosis (Fig. 17.2). The neoplasm may also demonstrate areas of tubular or solid growth, and these patterns rarely may predominate. Individual tumor cells are small to medium sized with inconspicuous cytoplasm, hyperchromatic nuclei, and one to few nucleoli. Mitotic activity within these tumors is typically low. Perineural invasion is seen in up to three quarters of cases (Fig. 17.3).

Immunohistochemical staining of these tumors will reveal cytokeratin positivity, with epithelial membrane antigen (EMA), and less

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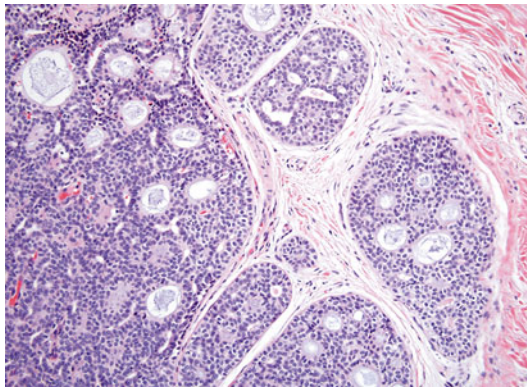

Fig. 17.1 Primary cutaneous adenoid cystic carcinoma. There are nests and islands of cytologically monotonous cells with cribriform architecture

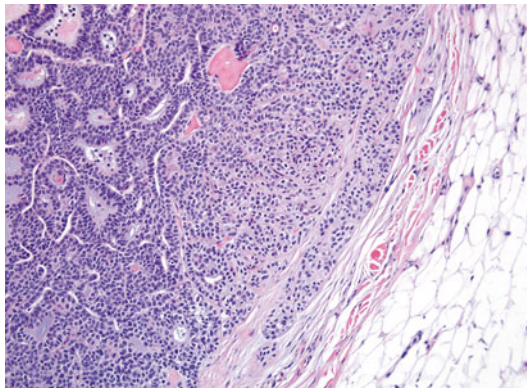

Fig. 17.2 Primary cutaneous adenoid cystic carcinoma. In areas, the growth pattern is more solid. Basement membrane material is focally present and provides a clue to diagnosis. This tumor has invaded the subcutis

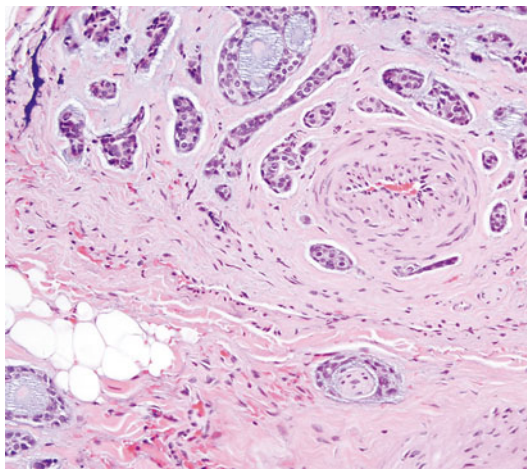

Fig. 17.3 Primary cutaneous adenoid cystic carcinoma. Perineural invasion is seen in a majority of cases and should be searched for diligently

consistently carcinoembryonic antigen (CEA) expression in areas of ductal differentiation. Myoepithelial differentiation is noted at least focally in these tumors, as seen with smooth muscle actin, calponin, and/or S100 protein staining in the cells surrounding the pseudoglandular spaces. Expression of p63 in the myoepithelial component is also reported. As in the salivary gland counterpart, CD117 (c-kit protein) is frequently expressed diffusely in tumor cells. The basophilic mucinous material within the pseudocystic tumor spaces stains with Alcian blue.

Differential Diagnosis

Metastasis or direct extension of adenoid cystic carcinoma from salivary gland or other site can be histologically identical and should be excluded clinically. Primary cutaneous cribriform apocrine carcinoma is likely the closest histological mimic to primary cutaneous adenoid cystic carcinoma. This low-grade malignancy arises more commonly on the extremities in a slightly younger age group. It is characterized histologically by exclusively cribriform architecture, variation in the sizes of pseudoglandular spaces, more cytologic pleomorphism, an absence of perineural invasion, and a lack of staining for myoepithelial markers. Primary cutaneous cribriform apocrine carcinoma has an indolent course with lower rates of local recurrence and negligible rates of metastasis than cutaneous adenoid cystic carcinoma, and thus the distinction between these two entities is important. Basal cell carcinoma with an adenoid pattern can be distinguished from adenoid cystic carcinoma by the presence of peripheral palisading and a connection to the epidermis. Additional entities within the differential diagnosis can include mucinous carcinoma, which will lack myoepithelial differentiation but will typically express hormonal receptors, and metastatic adenocarcinoma, particularly of breast origin, which will lack deposition of basement membrane-like material. Adenoid cystic-like patterns have been reported within spiradenomas and spiradenocylindromas and represent a potential pitfall in diagnosis if a lesion is only partially sampled.

Prognosis

In general, primary adenoid cystic carcinoma behaves more indolently than its salivary gland counterpart. A retrospective study based on SEER data estimated a 96 % five-year survival rate. However, local recurrence is not uncommon, occurring in approximately 50 % of cases, although metastatic spread is unusual. More aggressive behavior has been documented in primary adenoid cystic carcinoma arising from the Bartholin glands of the vulva, with high rates of perineural invasion, local recurrence, and an increased propensity for distant metastases to the lung. These adverse effects have been theorized to be related to the high density of nerves in this body site. Unlike salivary gland adenoid cystic carcinoma, histological grading of tumor based on the amount of solid-pattern morphology and mitotic activity did not correlate with recurrence rate or survival in a small series of cases of cutaneous adenoid cystic carcinoma for which outcome data were available.

Treatment

Surgical excision with wide margins is the treatment of choice. Given the propensity for this tumor to infiltrate and spread along nerves, Mohs micrographic surgery has been proposed as a method by which to achieve clear margins while minimizing tissue defects, although the possibility of discontinuous perineural invasion has led to a suggestion that an additional margin of tissue might be taken after margins are histologically cleared. Sentinel lymph node sampling has been reported in this tumor, but is not usually performed due to its low rate of lymph node metastasis. Local radiation and even local photodynamic therapy have been utilized as adjuvant treatment but are not well studied. Chemotherapy is generalized reserved for metastatic disease.

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Malignant Mixed Tumor of Skin

18

Jerad M. Gardner and Bruce R. Smoller

Introduction

Mixed tumor of the skin is an uncommon neoplasm of sweat gland origin that usually occurs on the head and neck of adults (although malignant mixed tumor is more common in the trunk or extremities). It bears histological similarity to salivary gland mixed tumors (also known as pleomorphic adenomas) in that it possesses an epithelial glandular component admixed with a myoepithelial/mesenchymal stromal component. Although usually benign, rare examples of mixed tumor of the skin may show malignant histological features and/or behave in an aggressive fashion giving rise to local recurrence and regional and distant metastases and resulting in tumor-related mortality. Fewer than 50 cases of malignant mixed tumor have been reported in the literature almost all of which are single case reports.

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Clinical Features

Malignant mixed tumor of the skin may occur at nearly any age, although the majority of cases arise in adults. In contrast to benign mixed tumors, malignant mixed tumor appears to be more common in women. Benign mixed tumors are most common on the head and neck, but the malignant counterpart more commonly presents on the trunk or extremities (foot being the most common site), although malignant examples in the skin of the head and neck have also been reported. Malignant mixed tumors clinically present as a nodule or mass with nonspecific features ranging from 2 to 10 cm in greatest dimension. The majority of tumors arise de novo, but several cases of benign mixed tumor undergoing subsequent malignant transformation have been reported.

Pathology

Malignant mixed tumor displays similar features to the benign counterpart being composed of epithelial cells arranged in nests, cords, and glands set within a myxoid and/or chondroid stroma (Figs. 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, and 18.7). Some cases that subsequently behave aggressively are deceptively bland histologically. Alternatively, some cases are so markedly atypical histologically that little if any residual benign mixed tumor component can be identified in the

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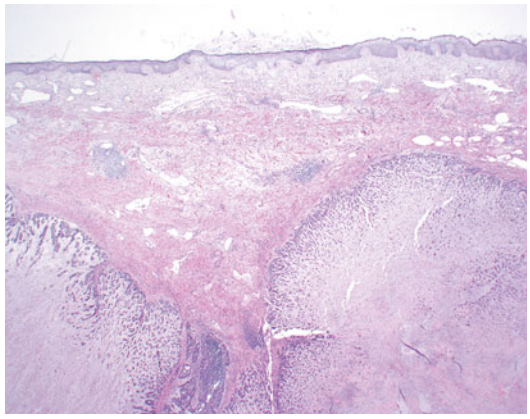

Fig. 18.1 Malignant mixed tumor displays dermal and/or subcutaneous nodules composed of epithelial cells arranged in cords and nests within a chondromyxoid stroma

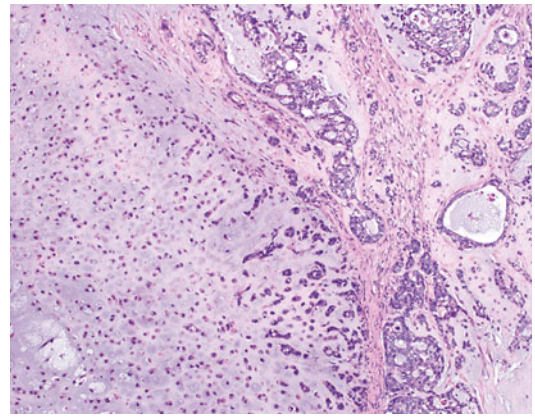

Fig. 18.4 The stroma may bear a remarkable similarity to cartilage

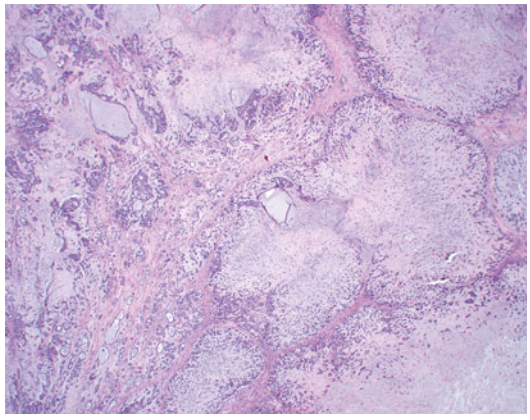

Fig. 18.2 The tumor has a multinodular architecture and prominent chondromyxoid stroma. Ductal differentiation is present in the lower left of the image

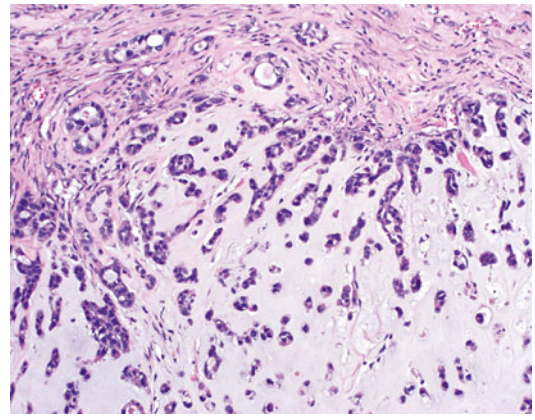

Fig. 18.5 The epithelial cells are arranged into nests with ductal differentiation or into cords and strands set within a chondromyxoid stroma

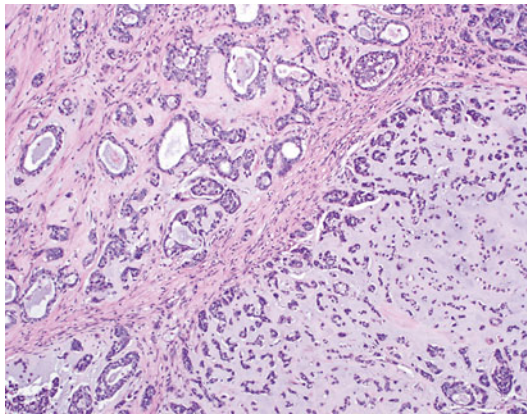

Fig. 18.3 The epithelial cells are arranged into nests with ductal differentiation or into cords and strands set within a chondromyxoid stroma

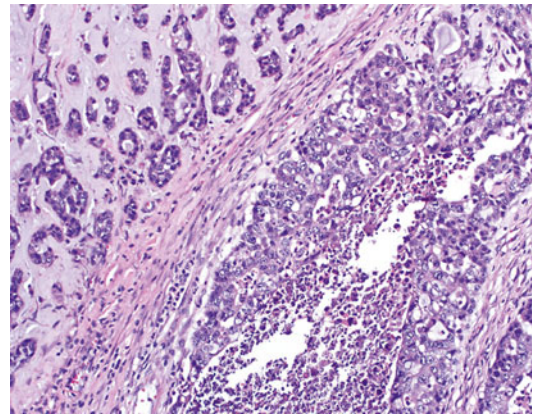

Fig. 18.6 Marked nuclear atypia and focal tumor necrosis may be present

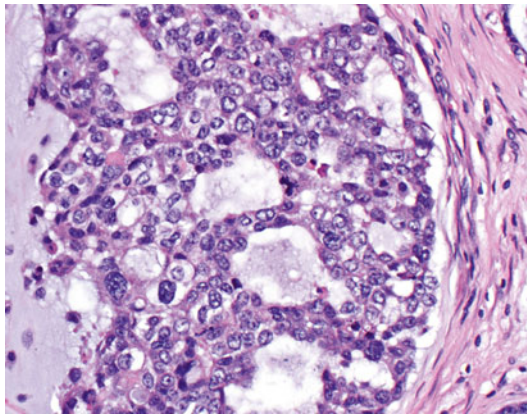

Fig. 18.7 Nuclear pleomorphism and atypical mitoses may be seen, although some cases of malignant mixed tumor are deceptively banal

background and the diagnosis of malignant mixed tumor can only be made based on the focal presence of myxoid or chondroid stroma. Other cases fall between these extremes and resemble benign mixed tumor but possess atypical histological features. Features suggestive of malignancy in mixed tumor include infiltrative growth pattern, nuclear pleomorphism, increased and/or atypical mitotic activity, tumor necrosis, and lymphovascular invasion (Figs. 18.6 and 18.7). The epithelial component of the tumor often expresses cytokeratins, epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA; stains luminal cells in glandular areas) by immunohistochemistry. The myoepithelial cells in the stromal component typically co-express cytokeratin and S100 protein and may also express other myoepithelial markers such as glial fibrillary acidic protein (GFAP).

Differential Diagnosis

The main histological differential diagnosis includes benign mixed tumor for banal-appearing malignant mixed tumors and other forms of poorly differentiated carcinoma for markedly atypical-appearing malignant mixed tumors. Other entities in the differential diagnosis include mucinous eccrine carcinoma, sarcomatoid carcinoma (carcinosarcoma) with chondrosarcomatous areas, matrix producing melanoma, metastatic chondrosarcoma, chondroma of soft parts, extraskeletal myxoid chondrosarcoma, ossifying fibromyxoid tumor of soft parts, and extra-axial soft tissue chordoma. Myoepithelioma and myoepithelial carcinoma have similar features to both benign and malignant mixed tumors; myoepithelial neoplasms and mixed tumors may exist on a spectrum.

Prognosis

Malignant mixed tumor of the skin is a relatively aggressive tumor that exhibits local recurrence, regional metastasis, and distant metastasis in nearly half of cases. Despite the high rate of metastasis, malignant mixed tumor may have a slow progression and prolonged course. Metastases may present after many years. The most common sites of distant metastases are lung and bones, but widely disseminated metastases may be seen in the end stage of the disease. The overall mortality is approximately 25 %.

Treatment

As this is a rare tumor, there is no therapeutic standard of care for malignant mixed tumor of the skin. Complete surgical excision with wide margins has been suggested as the mainstay of treatment. Subsequent clinical and radiologic follow-up may be useful to detect local recurrence or nodal and/or distant metastases. Chemotherapy and radiotherapy do not appear to provide benefit to cases in which complete surgical excision has been obtained, but these modalities may be attempted in advanced cases.

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Hidradenocarcinoma

19

Franco Rongioletti

Introduction

Hidradenocarcinoma, first reported by Keasby and Hadley in 1954, refers to the malignant counterpart of hidradenoma and may be of apocrine or eccrine lineage. It is a rare neoplasm accounting for 6 % of malignant eccrine tumors.

Clinical Features

It presents as a reddish nodule, sometimes ulcerated, with a predilection for the head, face, and extremities in the sixth decade of life. However, it may involve any site including the scalp (Fig. 19.1), neck, chest, back, leg, toe, and vulva. A pyogenic granuloma-like presentation may also occur. Rarely, some cases have been reported in children and also at birth. Malignant transformation from a benign hidradenoma is admitted.

Pathology

The tumor is characterized by a dermal nodular or nodulocystic infiltrative pattern of growth composed of epithelial sheets with a typical clear cell change (Fig. 19.2). The epithelial cells may have also a squamoid or basaloid appearance. Rarely, mucinous differentiation is evident. Central necrosis within lobular epithelial aggregates is sometimes present (comedo variant) (Fig. 19.3). A characteristic feature is the presence of well-developed ducts (Fig. 19.4). Although the tumor may have a deceptively bland appearance, the cells show mitotic activity and nuclear pleomorphism. Perineural infiltration may be found (Fig. 19.5). Pagetoid cells can be identified in the overlying epidermis. The tumor stains with antibodies to keratin AE1/3, cytokeratin 5/6, Ki67, and p53 and may be positive for CEA, EMA, and GCDFP-15. Moreover, like other skin tumors with eccrine differentiation, it also expresses positive staining for estrogen and progesterone receptors. Rarely, hidradenocarcinomas show a t(11;19) translocation and the amplification of the Her2/neu gene.

Differential Diagnosis

Histologically, hidradenocarcinoma should be distinguished from other microscopic clear cell tumors such as clear cell squamous carcinoma, trichilemmal carcinoma, and renal metastatic

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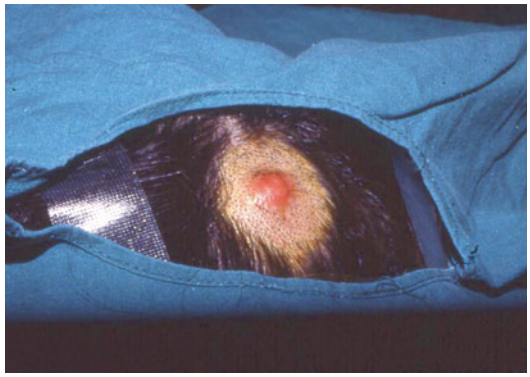

Fig. 19.1 Hidradenocarcinoma. A *reddish* nodule on the scalp. The diagnosis is a histological one

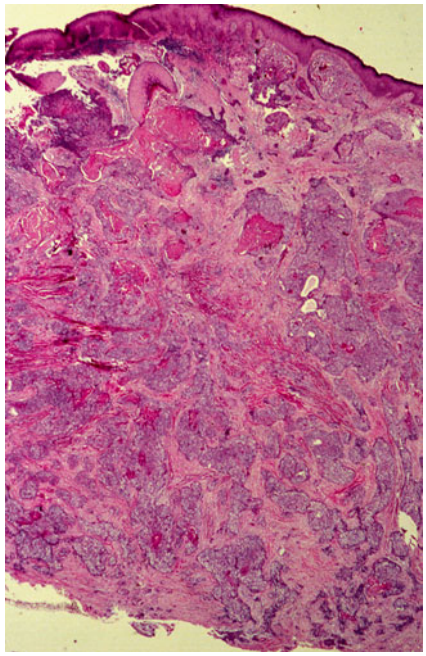

Fig. 19.2 A nodular dermal growth composed of epithelial sheets with squamoid areas and ductal differentiation

clear cell carcinoma. Clear cell squamous cell carcinoma and trichilemmal carcinoma can be distinguished by the absence of ductal structures as well as negativity for EMA and CEA. Metastatic renal cell carcinoma is positive for EMA and renal cell antigen but negative for CEA.

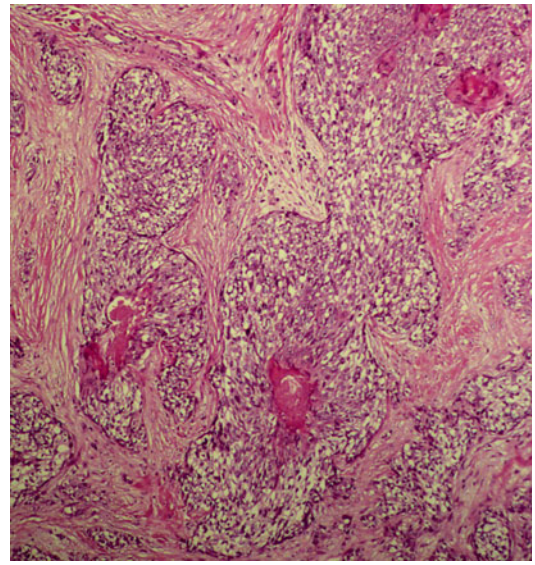

Fig. 19.3 Islands of epithelial sheets with a typical clear cell change, squamoid differentiation and central necrosis

Prognosis

Hidradenocarcinoma is a very aggressive neoplasm with a high rate of recurrence (>50 %) and eventual distal metastases to lymph nodes, bones, lungs, and skin itself (60 %). The prognosis for 5-year disease-free survival is poor with less than 30 % of patients. Although an inverse relationship between tumor size and survival has been observed, metastases can arise from large as well as small lesions and typically appear first in regional lymph nodes. Lymph node biopsy has been used to detect subclinical metastases to regional lymph nodes.

Treatment

Considering the high rate of local recurrence and metastasis, early wide surgical excision with at least 2 cm of clear margins is the treatment of choice. The efficiency of adjuvant radiotherapy and chemotherapy has not been established.

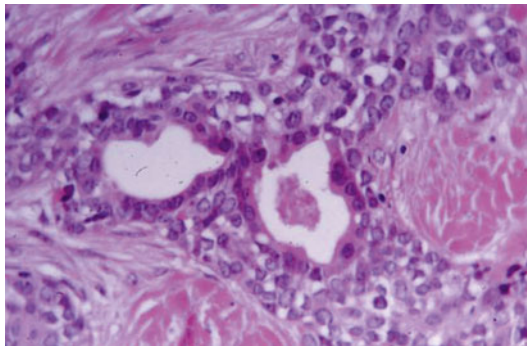

Fig. 19.4 A characteristic feature is the presence of well-developed ducts

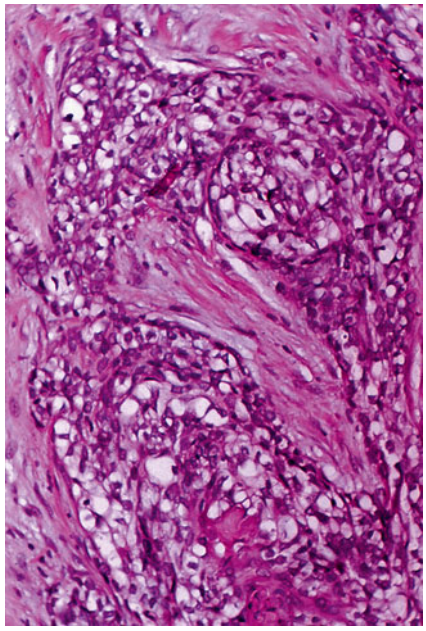

Fig. 19.5 Perineural infiltration may be found. Note clear cell change

Efficacy of capecitabine has been reported in metastatic cases. The utility of antiestrogen chemotherapy and trastuzumab (a humanized murine antibody that antagonizes Her-2/*neu* receptor) is under investigation in metastatic sweat gland carcinomas.

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Malignant Cylindroma

20

Valentina Caputo and Franco Rongioletti

Introduction

Malignant cylindroma (MC) is an extremely rare adnexal tumor, firstly described by Wiedemann in 1929 with less than 40 documented cases in literature. It is a high-grade neoplasm with aggressive behavior, characterized by locally infiltrative growth and metastatic potential. Histopathologically, the diagnosis is possible only on the basis of the presence of foci of benign preexisting cylindroma. Malignant transformation may arise in solitary cylindromas or, more commonly, in the setting of the autosomal dominant Brooke-Spiegler syndrome, characterized by the development of adnexal tumors, mostly cylindromas, but also trichoepitheliomas and spiradenomas. Etiopathogenesis is controversial, but some reported cases have been described following radiotherapy, and mutations of the tumor suppressor gene CYLD have been demonstrated in Brooke-Spiegler syndrome.

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Clinical Features

MC generally presents as a rapidly growing solitary, intradermal, sometimes ulcerated, round to oval, tender to firm in consistency, reddish to purple-blue-colored nodular tumor of the scalp, although the face, the trunk, and the extremities may be affected. Size may range from few to several centimeters (>10). Most patients are in their seventh to ninth decade of life, with a slight female predominance.

Pathology

Histopathologically, the tumor is composed of dermal irregular cords and nests of highly atypical and pleomorphic cells, sometimes showing ductal differentiation and cysts formation, and is characterized by an infiltrative pattern of growth, without connection to the epidermis (Figs. 20.1 and 20.2). Atypical mitotic figures and necrosis with perineural invasion are often present (Fig. 20.3). Scattered throughout the tumor are residual benign cylindromatous foci, characterized by a dual cell population organized into basaloid islands, surrounded by a hyaline, thick, PAS-positive basal membrane with the typical "jigsaw" pattern (Fig. 20.4). Tumor cells express immunohistochemical positivity to CAM 5.2 and EMA and to CEA in tubular structures, while positivity to S100 and GCDFP-15 is variable. Despite the fact that

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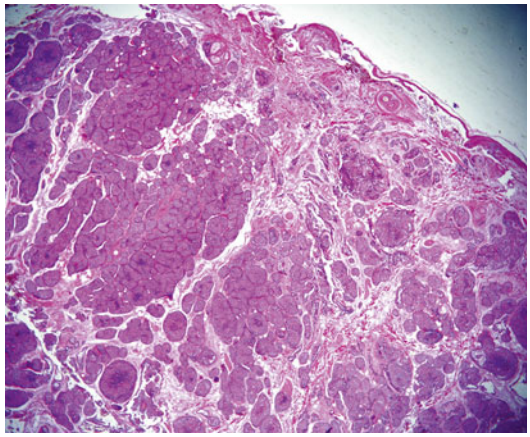

Fig. 20.1 Malignant cylindroma. The tumor is composed of dermal irregular cords and nests with an infiltrative pattern of growth, without connection to the epidermis

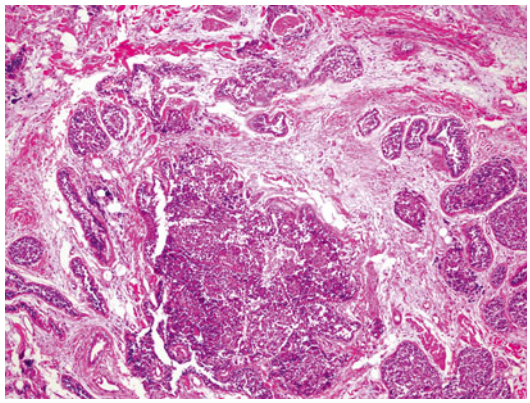

Fig. 20.2 The tumor forms expansile nodules, sometimes showing ductal differentiation

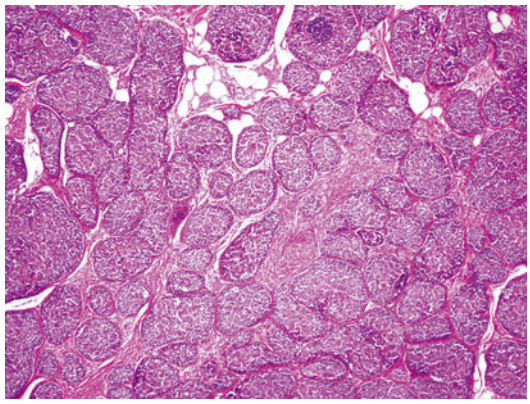

Fig. 20.3 Scattered throughout the tumor are residual benign cylindromatous foci, characterized by a dual cell population organized into basaloid islands, surrounded by a hyaline, thick, basal membrane with the typical "jigsaw" pattern

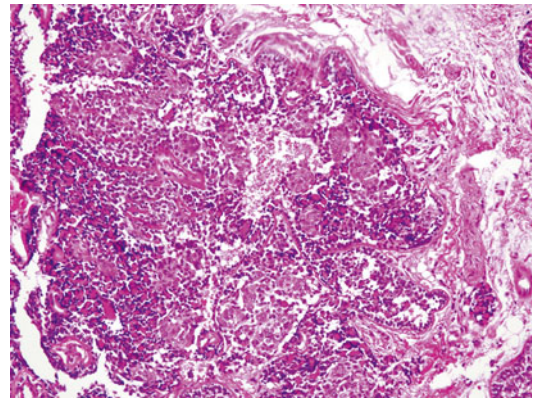

Fig. 20.4 The tumor reveals areas with atypical cells, loss of the dual population and necrosis

most MC represent high-grade adenocarcinomas, occasional tumors may show squamous and spindle cell differentiation. One case of carcinosarcoma arising in a patient with Brooke-Spiegler syndrome has been reported in literature.

Differential Diagnosis

The diagnosis is a histological one and depends on the recognition of preexisting benign cylindromatous foci.

Prognosis

MC is a high-grade neoplasm, with a recurrence rate of 36 % and a metastasis rate of 46 %, with involvement mainly of the lymph nodes, liver, lung, and bones.

Treatment

Wide surgical excision with adequate margins has to be considered the treatment of choice, while high-dose radiation is an option suggested to treat inoperable tumors.

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Malignant Eccrine Spiradenoma

21

Valentina Caputo and Franco Rongioletti

Introduction

Malignant eccrine spiradenoma (MES) is an extremely rare aggressive tumor, firstly reported in 1972 by Dabska that can occur de novo or more commonly arise on a preexisting often long-standing eccrine spiradenoma. The latency period before malignant transformation ranges from 6 months to 70 years. To date, about 102 cases have been reported, mostly as single case report.

Clinical Features

MES typically presents as a rapidly growing, sometimes ulcerated, tender to firm in consistency, reddish-blue nodule or mass, often originating within a long-standing preexisting lesion. The average age of the disease occurrence is 59 years (range 21–92 years) without prevalence of sex. The trunk and extremities are the preferential sites (92 % of reported cases) (Fig. 21.1); less frequently the scalp, the neck, and other unusual areas such as the external auditory canal, the vulva, and the breast have been reported. Size may range from few to several centimeters (>10) at the time of diagnosis.

Pathology

Histopathological diagnosis of MEC requires the detection throughout the tumor, of at least one focus, variably represented, of benign eccrine spiradenoma, with the typical dual cell population, arranged in nests and trabeculae (Figs. 21.2 and 21.3). The malignant features are not specific and include solid aggregates of tumor cells with mild to moderate nuclear atypia, loss of two cell populations, an infiltrative pattern of growth, atypical mitotic figures, necrosis, lymphovascular, and perineural invasion (Figs. 21.4 and 21.5). Other features are invasion of surrounding connective tissue, loss of basement membrane, squamous differentiation, and clear cell, oncocyte-like, and sarcomatoid changes. "Sarcomatous" or "squamous" changes seem significantly to be correlated with a poorer prognosis. Two distinct morphological patterns of MEC have been described, the most common form consisting of an obviously malignant pleomorphic tumor (high-grade carcinoma) and a second low-grade

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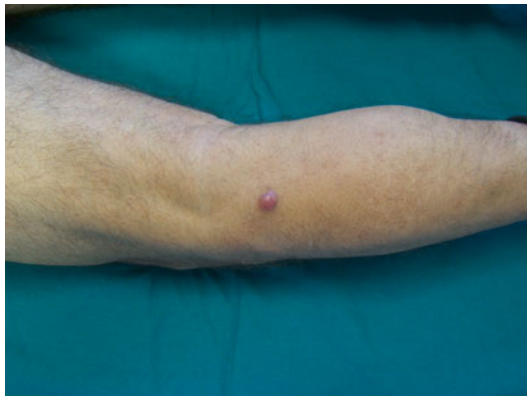

Fig. 21.1 A rapidly growing, firm in consistency, *reddish-blue* nodule on the forearm

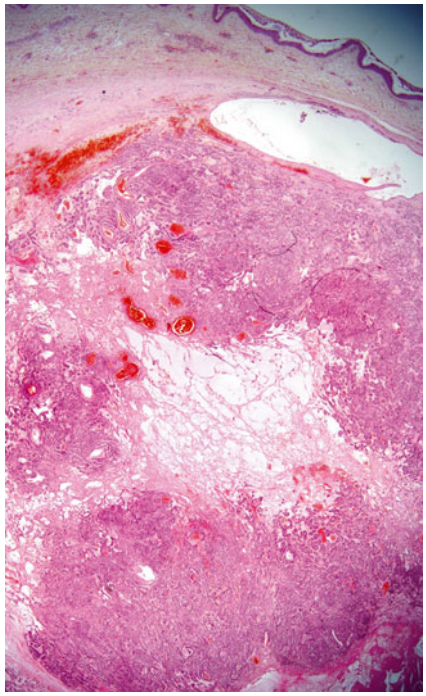

Fig. 21.2 A basaloid nodular proliferation without epidermal connection

form that closely mimics benign spiradenoma. Some malignant tumors showing features of both spiradenoma and cylindroma are named "spiradenocylindrocarcinoma." These features support the evidence that both tumors are derived from a common pluripotential basal cell line.

Immunohistochemistry may be helpful in highlighting ductal structure which is EMA and

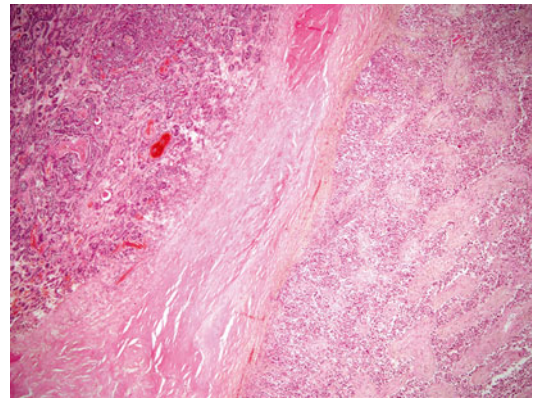

Fig. 21.3 An area with carcinoma (*right*) adjacent to a benign eccrine spiradenoma (*left*)

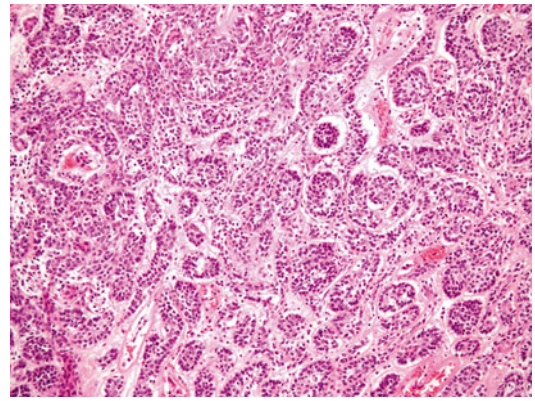

Fig. 21.4 The tumor is composed on nests and cords with loss of the dual population

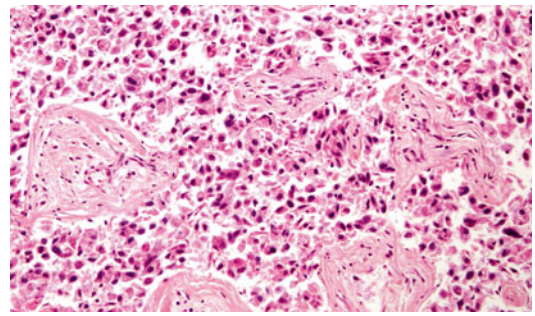

Fig. 21.5 Malignant features with aggregates of tumor cells with mild to moderate nuclear atypia, necrosis, lymphovascular, and perineural invasion

CEA positive, while the background population results positive to S100, EMA, Cam 5.2, and occasionally estrogen.

Differential Diagnosis

The diagnosis of MES is mainly a histological one and relies on the detection of foci of benign spiradenoma. Differential diagnosis should include other adnexal neoplasm such as cylindromas, malignant nodular hidradenoma, and basal cell carcinoma. Anaplastic carcinoma, adenocarcinoma, squamous cell carcinoma, and carcinosarcoma should also be considered.

Prognosis

MES is considered as an aggressive tumor, with a reported recurrence rate of 57 %, metastasis rate of 39 %, and mortality rate of 20 %; 17.5 % of patients with metastatic diseases die after an average time period of 11 months following diagnosis.

Treatment

Although there is no established consensus on the treatment regimen, wide excision with 1 cm, tumor-free, circumferential, and deep margins down to the fascia has been recommended, while high-dose radiation and adjuvant chemotherapy do not seem to improve survival in patients with inoperable or recurrent tumors. Sentinel node excision has been proposed, but the results of elective lymph node dissection are questionable. In addition to regional lymph nodes, metastases involve the lung, liver, brain, spinal cord, bone, and skin.

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Part IV

Tumours of Eccrine Gland

Microcystic Adnexal Carcinoma

22

Irina Margaritescu and A. Doru Chirita

Introduction

Microcystic adnexal carcinoma (MAC), first described by Goldstein et al. in 1982, represents a distinctive malignant neoplasm with an indolent, locally destructive behavior. The neoplasm has a predilection for the face and is composed of cornifying cystic structures in the upper portion, columnar and solid aggregations of pale or slightly dark eosinophilic epithelial cells in the middle, and duct-like or tubular structures in the lower part. The neoplasm manifests both sweat gland and follicular differentiation.

Clinical Features

The tumor typically appears in middle-aged to elderly patients. However, the age at diagnosis ranges from 6 to 90 years, with only a few cases reported in children. One case has been documented to be present since birth. Men and women are almost equally affected. MAC usually occurs on the head and neck. The most common affected area is the centrofacial region (upper and lower lip, nasolabial fold, nose, chin, cheek, and eyebrow). Occasionally, the tumor may appear on the scalp, forehead, orbit, ear, chest, axilla, buttocks, genitalia, palm, and toe. The lesion may present as a slowly enlarging, flesh-colored, yellow or erythematous, solitary, indurated papule or plaque (Fig. 22.1). The tumor has ill-defined margins that extend several centimeters beyond the clinically visible limits. The size of the tumor usually ranges from 0.25 to 2.5 cm in diameter, but larger tumors up to 12 cm in diameter have also been reported. The lesion is usually asymptomatic. Advanced lesions may present with numbness, burning, stinging, anesthesia, or paresthesia due to perineural infiltration. The correct diagnosis is usually delayed due to its indolent growth and clinical resemblance to a benign lesion. The time delay from first detection of the tumor to diagnosis varies and ranges from several months to 50 years.

Pathology

At scanning magnification, MAC has a silhouette of a malignant neoplasm, being large, asymmetrical, and poorly circumscribed and usually extending deep into the dermis and subcutaneous

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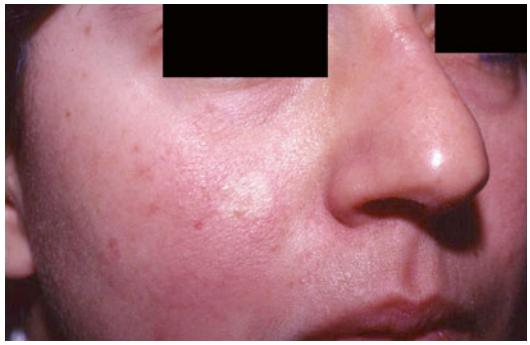

Fig. 22.1 A slowly enlarging, flesh-colored, indurated plaque with ill-defined borders on the face

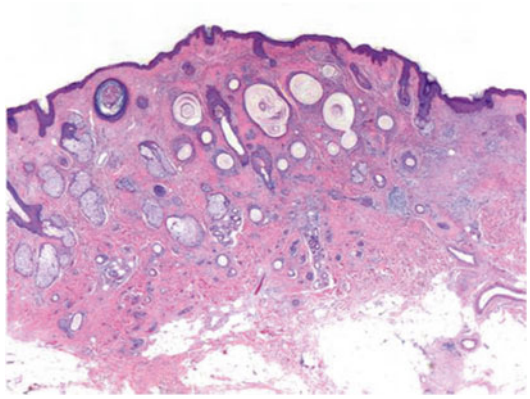

Fig. 22.2 The neoplasm has a characteristic appearance with cornifying cystic structures in the superficial part of it, and solid aggregations of epithelial cells admixed with tubular structures in its deeper aspects

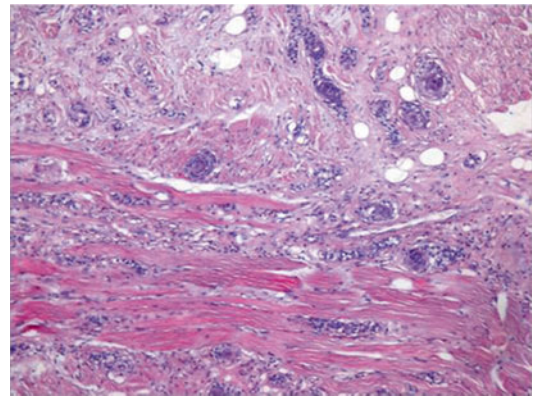

Fig. 22.3 The tumor usually extends into the subcutaneous fat and sometimes into the skeletal muscle. Tubules or cysts with tadpole-like morphology may occasionally be seen

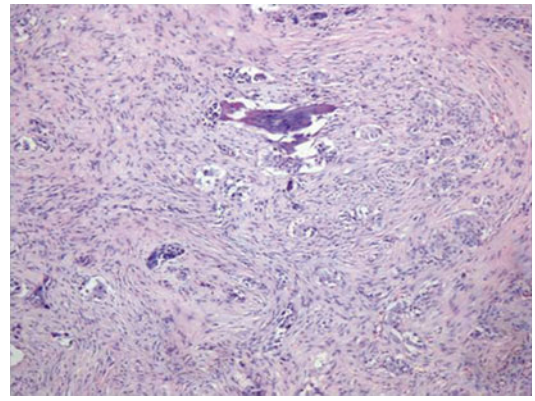

Fig. 22.4 MAC is notorious for its infiltrative and destructive growth. This neoplasm shows extension into the sphenoid sinus. The tumor is embedded into a desmoplastic stroma

fat and sometimes into the fascia, skeletal muscle, and bone (Figs. 22.3 and 22.4). The neoplasm has a characteristic appearance with cornifying cystic structures lined by squamoid cells in the superficial portion, solid aggregations of cells with pale or slightly dark eosinophilic cytoplasm in the middle part, and tubular structures lined by one or two layers of cuboidal cells that contain homogeneous eosinophilic material in the deeper aspects of the tumor (Fig. 22.2). These components are not always present and frequently may overlap. Some cases show a preponderance of solid structures with few if any cornifying cystic and tubular structures. Other cases show a predominance of tubular structures and may overlap with syringoid eccrine carcinoma. Tubules or cysts with tadpole-like morphology may occasionally be seen. There is no connection with the epidermis, but some examples show attachment to preexisting infundibula. Clear cell change, foci of decapitation secretion, sebaceous differentiation, and small whorls of

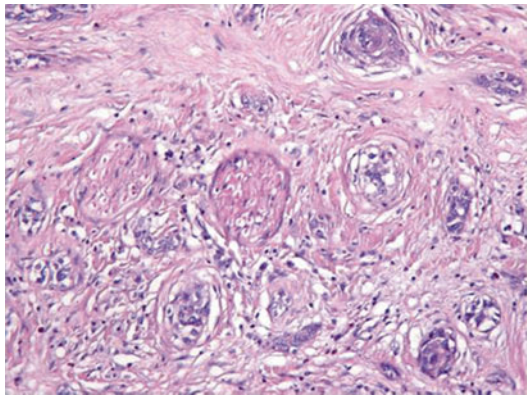

Fig. 22.5 The nuclei of neoplastic cells are mainly small and monomorphous and lack nuclear atypia and mitotic figures. Frequently, the neoplasm manifests perineural involvement

compactly organized blue-gray corneocytes suggesting inner sheath differentiation may be seen.

The nuclei of the neoplastic cells are mainly small and monomorphous and usually lack nuclear atypia and mitotic figures. Frequently, the neoplasm manifests perineural involvement (Fig. 22.5). The epithelial component is disposed in a variably hyalinized stroma with thickened collagen bundles.

Immunohistochemistry

The tumor cells express AE1/AE3, AE13/AE14, CK15, CD15, and Ber-EP4. Ductal differentiation and intracytoplasmic lumen formation are highlighted by EMA and CEA.

Differential Diagnosis

MAC can be differentiated from syringoma, especially the plaque-type syringoma, and from desmoplastic trichoepithelioma and trichoadenoma by its deep and infiltrative growth pattern and perineural infiltration. Presence of keratocysts, nuclear atypia, and mitosis are features that militate against syringoma, and the presence of ductal differentiation excludes desmoplastic trichoepithelioma and trichoadenoma. Morpheaform basal cell carcinoma and desmoplastic squamous cell carcinoma usually lack ductal differentiation and intracytoplastic lumen formation and zonation from the epidermis. Metastatic adenocarcinoma lacks keratocyst formation and is typified by more pleomorphism and cytologic atypia. TTF1 expression aids in the distinction of metastatic microcystic squamous cell carcinoma of the lung from MAC. Childhood MAC should be differentiated from extraordinary cases of diffuse atrophoderma vermiculata of the head and neck, Nicolau-Balus syndrome, Rombo syndrome, and multiple eccrine-pilar hamartoma syndrome. These proliferations lack perineural infiltration and have a distinctive histological appearance with epithelial strands embedded in concentric fibrotic rings and ball-like aggregations of elastic fibers in the papillary dermis. MAC may arise in association with multiple benign syringomatous proliferations, which may make the surgical management of it challenging. However, benign syringomatous proliferations are discrete focal proliferations of eccrine ducts in the upper reticular dermis and lack deeper extension and perineural invasion.

Prognosis

MAC is a locally aggressive and destructive tumor due to its infiltrative growth pattern with frequent extension into subcutis and muscle, and sometimes even bone. Perineural invasion is a common finding. Exceptional cases of orbital involvement as a primary presentation or as a direct extension of the tumor have been reported (Fig. 22.6). Very sporadic cases of MAC with lymph node or distant metastases (to the lung, liver, or bone) have been documented. However, MAC may have a good prognosis with a low recurrence rate when Mohs micrographic surgery is used.

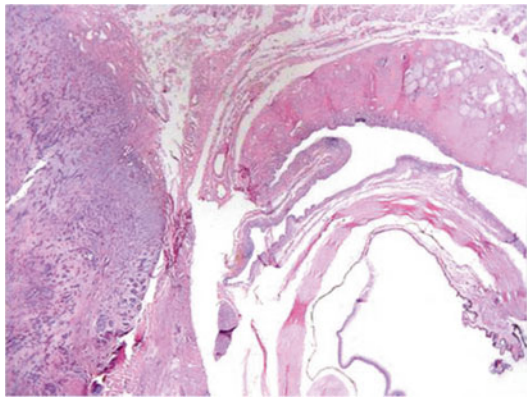

Fig. 22.6 Besides direct extension into the orbit, this tumor also involved the frontal, ethmoidal, and sphenoid sinuses with dura mater invasion

Treatment

The current treatment of choice for MAC is Mohs micrographic surgery. Radiation therapy, either as a primary therapy or as adjuvant to surgery, may provide some benefit in complicated or inoperable cases. However, some tumors are radioresistant. Moreover, radiation exposure was also reported as a cause of MAC in a significant proportion of cases.

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Syringoid Eccrine Carcinoma

23

Franco Rongioletti

Introduction

Syringoid eccrine carcinoma (SEC) and sclerosing sweat duct carcinoma are the most common terms used to name a rare malignant adnexal tumor that is considered by most of the papers in the literature as synonymous with microcystic adnexal carcinoma (MAC). In this chapter, SEC is treated as if it were not the same entity as MAC but rather a variant of MAC without folliculocystic structures and with more prominent ductal differentiation.

Clinical Features

SEC has a predilection for female greater than 60 years of age. The neoplasm involves the head and neck region with a predilection for centrofacial area (about 85 % of cases) (Fig. 23.1). Less frequent sites include the axilla, trunk, and extremities (Fig. 23.2). The clinical presentation is that of a subcutaneous indurated nodule or plaque-like lesion with pink- or yellow-colored, ill-defined margins and overlying telangiectasia. The epidermis may be normal, atrophic, or scaly. Ulceration is uncommon.

Pathology

The histological appearance includes an infiltrative growth pattern with formation of tubules, small elongated nests and cords, syringoma-like tadpole structures embedded in a desmoplastic stroma (Figs. 23.3, 23.4 and 23.5). These structures are lined with a double layer of cells with flattened cuboidal or squamous differentiation. There is prominent squamoid differentiation, most apparent superficially, where neoplastic aggregates are larger and composed of epithelial cells with abundant amphophilic cytoplasm. Cellular atypia and mitoses are generally mild to moderate. Perineural and intraneural invasion is a characteristic finding. This tumor extends deep into the dermis, subcutis, and skeletal muscle and sometimes into the bone. The tumor cells express typically cytokeratin AE1/AE3, CAM 5–2, Leu M1, CEA (Fig. 23.6), and PS100.

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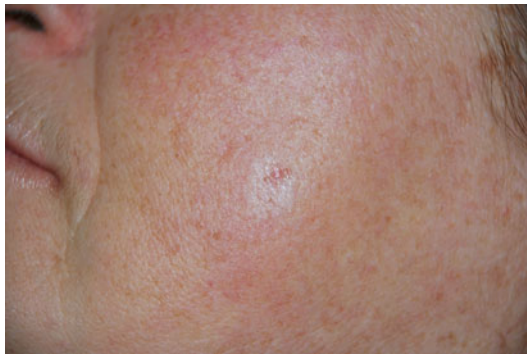

Fig. 23.1 Syringoid eccrine carcinoma. An indurated withish plaque on the cheek

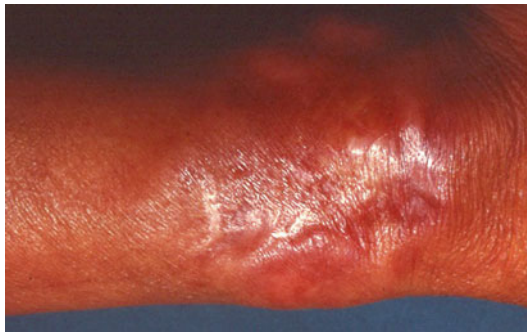

Fig. 23.2 Syringoid eccrine carcinoma. An infiltrated plaque with ill-defined margins on the wrist

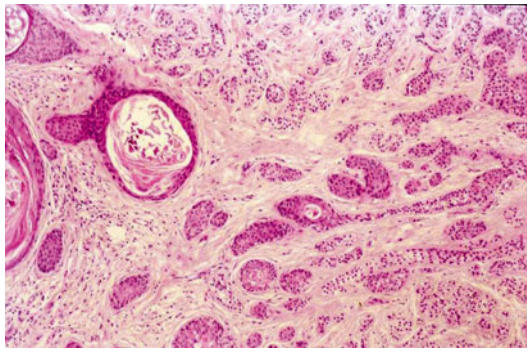

Fig. 23.3 An infiltrative proliferation composed of small elongated nests and cords, squamoid islands with keratinous cyst and syringoma-like tadpole structures with clear cell changes embedded in a desmoplastic stroma

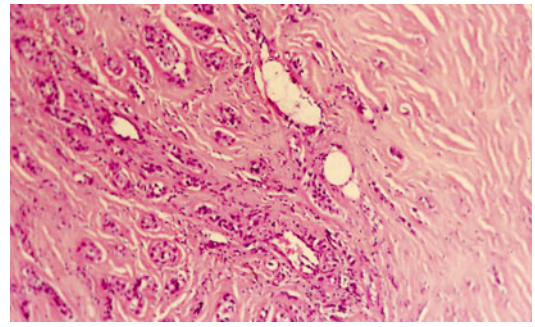

Fig. 23.4 Small elongated nests and cords with duct-like structures in a desmoplastic stroma

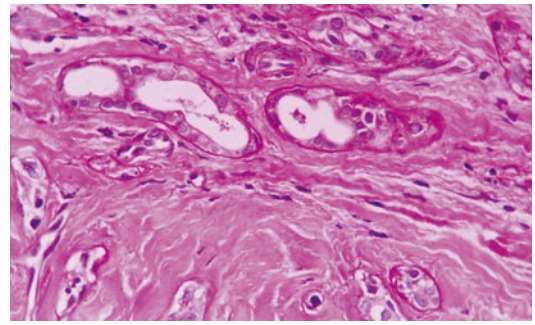

Fig. 23.5 Small nests and cords with ductal differentiation (PAS stain)

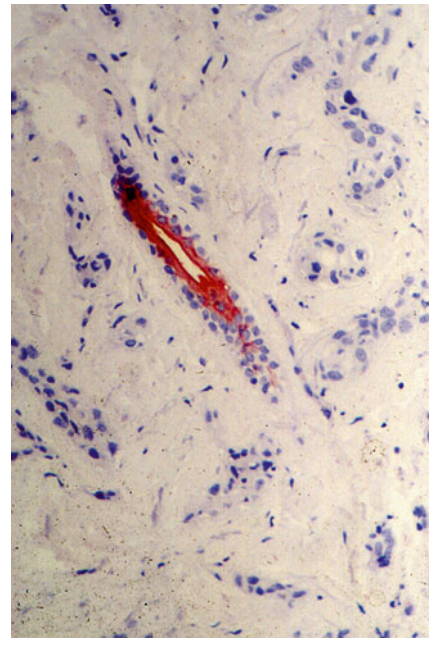

Fig. 23.6 CEA stain highlights the ductal differentiation

Differential Diagnosis

The histological diagnosis of this tumor is difficult when the biopsy is of small size or superficial or when the characteristic histological features are not apparent. The differential diagnosis mainly concerns syringoma, desmoplastic trichoepithelioma, squamous cell carcinoma, sclerodermiform basal cell carcinoma, trichoadenoma, cutaneous metastasis of breast carcinoma, and a traditional MAC. Although SEC and MAC are likely closely related, the latter typically shows a more biphasic appearance, with prominent superficial keratocysts and deeper small diffusely infiltrative cords and ductal structures. On the contrary, SEC exhibits a uniform appearance showing smaller, more infiltrative-appearing deeper cords and ducts without keratocyst formation.

Prognosis

The invasive tumor is locally destructive with high rate of recurrences ranging from 30 to 47 %. Relapse may occur at the primary site even after a long disease-free interval of 30 years. Lymph node and distant metastasis are rare.

Treatment

Complete surgical excision is the treatment of choice with a surgical margin of 2 cm. Radiotherapy is rarely applied because this tumor is radioresistant. In the literature, about 40–60 % of patients had one or more local recurrences within 6 months to 30 years after treatment with standard wide local excision. Mohs micrographic surgery is considered a best treatment to avoid relapses.

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Digital Papillary Adenocarcinoma

24

Franco Rongioletti

Introduction

Digital papillary adenocarcinoma (ADPC) is a rare sweat gland tumor predominantly involving the distal end of digits first described by Helwig in 1984. Although an adenomatous form has been described, the current trend is to consider that all cases be referred to as ADPC as the histological grading cannot accurately predict recurrence and metastasis. White males are predominantly affected with a mean age of 43 years, but it has also been described in young people. The tumor is considered to be of eccrine differentiation mostly because it is located on eccrine-rich sites. However, some authors have found decapitation secretion as a feature, which would indicate apocrine differentiation.

Clinical Features

The neoplasm presents as a firm, tan-gray to white-pink, rubbery papule or nodule or a cyst-like lesion of a few millimeters up to 2 cm in diameter, almost exclusively located on the volar surface of the fingers and toes and occasionally on the palms and soles. Lesions are often slow growing and painful, but they can have an indolent clinical course without symptoms. The diagnosis is usually not clinically suspected, and the tumor is often considered as a benign lesion as a cyst. It may also present as a simple nail bed infection.

Pathology

A multinodular solid and/or cystic proliferation with papillary projections infiltrating the dermis and subcutaneous tissue is seen (Fig. 24.1a, b). Involvement of the underlying bone may occur. Tubular structures lined by cuboidal or columnar epithelium, surrounded by an outer myoepithelial layer, are present at least focally within the solid component (Fig. 24.1b, c). Cytologic atypia, mitotic figures (Fig. 24.2a, b), and focal necrosis can be seen, but the histopathologic grading is not helpful in differentiating tumors with a more aggressive biological behavior as cases with minimal atypia may develop metastatic disease. Tumor cells are diffusely positive for MNF116 (Fig. 24.3a), while CEA (Fig. 24.3b) and EMA highlight the luminal border of tubules. A myoepithelial layer around tubular/glandular structures is positively stained with smooth muscle actin (SMA) and calponin. The intensity of Ki67 expression in tumor cells may be a marker of aggressive behavior (Fig. 24.3c).

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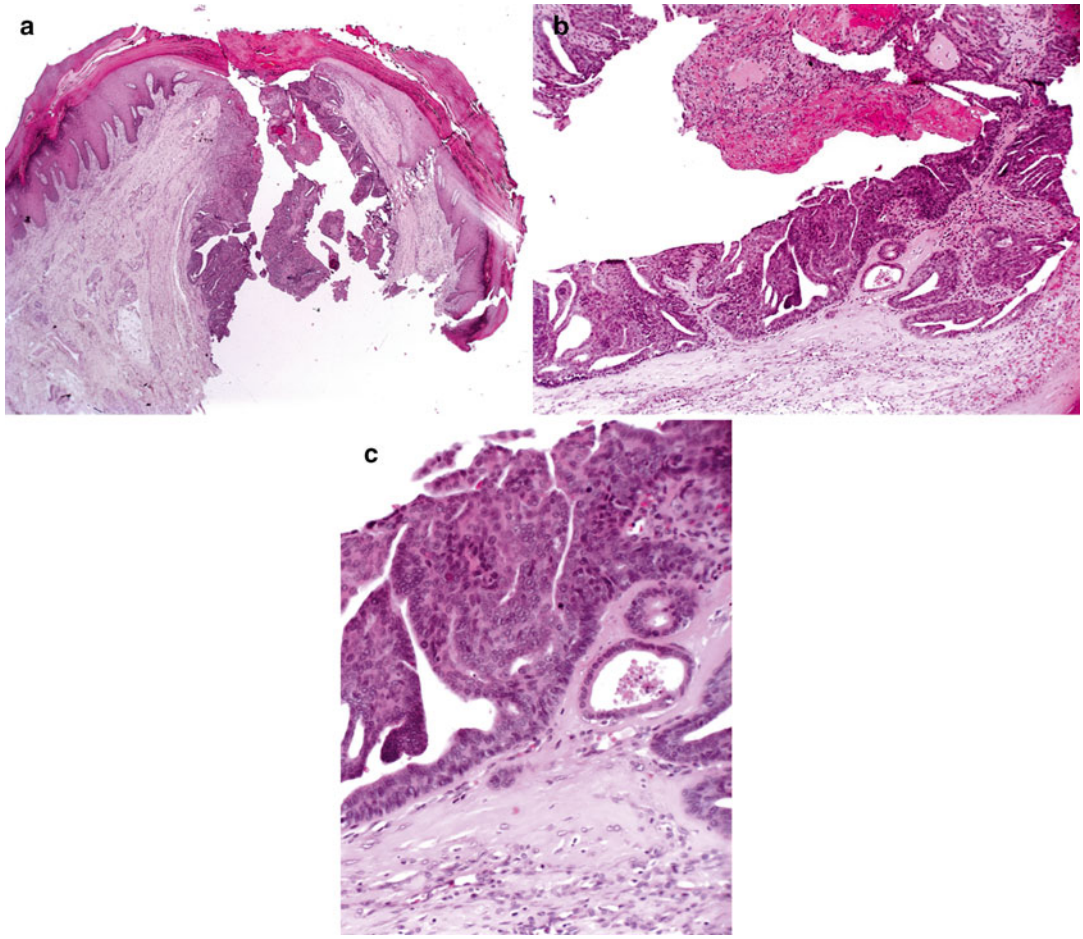

Fig. 24.1 (**a**) A nodular cyst-like proliferation with papillary projections infiltrating the dermis. (**b**) Papillary projections with tubular structures lined by cuboidal or columnar epithelium. (**c**) The glandular differentiation

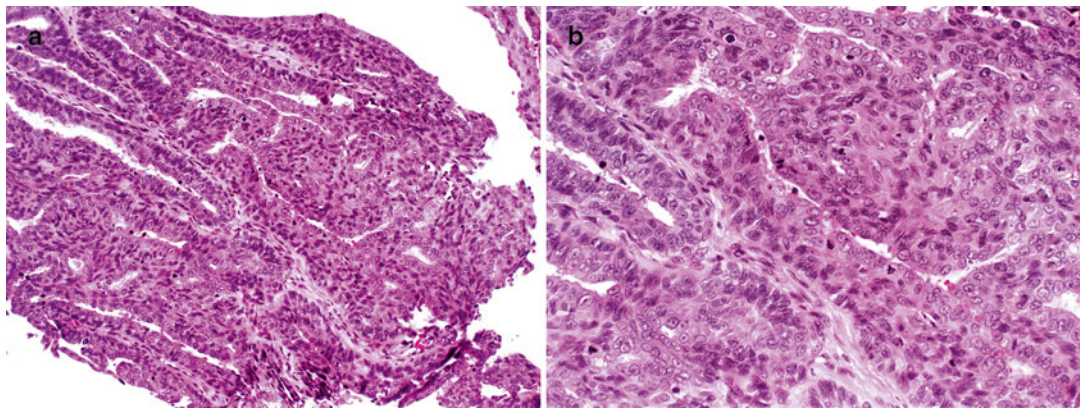

Fig. 24.2 (**a**) Cytologic atypia within solid areas. (**b**) Cytologic atypia with numerous mitoses

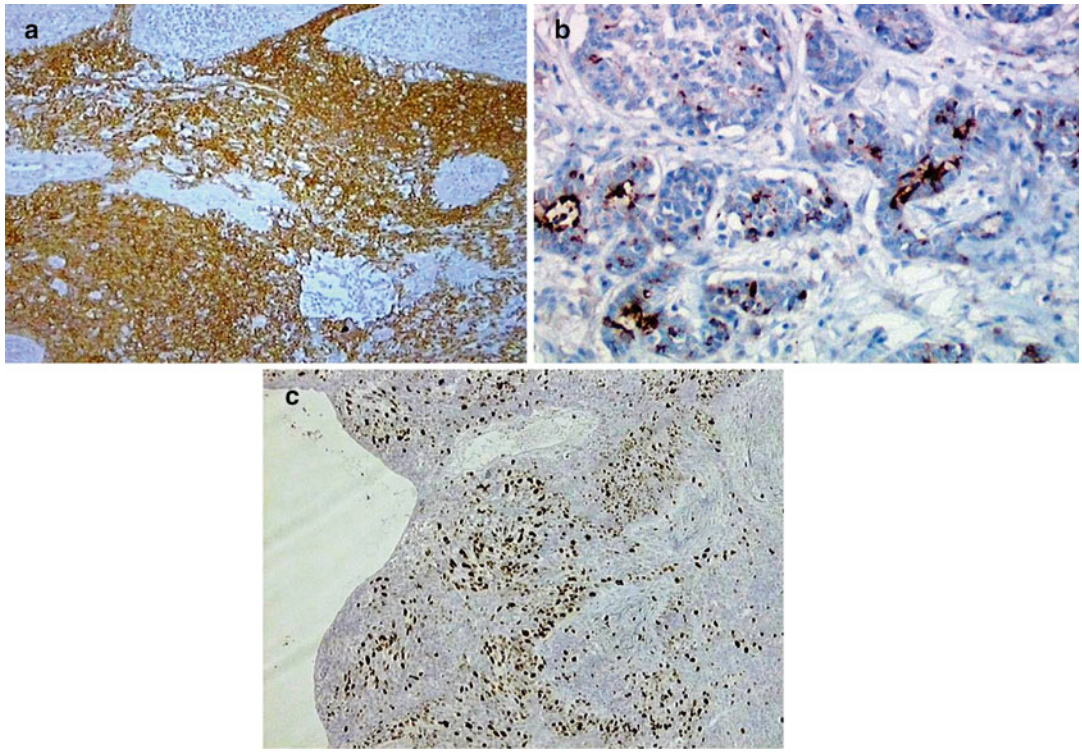

Fig. 24.3 (**a**) The tumor cells are diffusely positive for MNF116. (**b**) CEA highlights the luminal border of tubules. (**c**) The intensity of Ki67 expression is a marker of aggressive behavior

Differential Diagnosis

ADPC should be differentiated from benign adnexal tumors such as hidradenoma, papillary eccrine adenoma, tubular apocrine adenoma, apocrine cystadenoma, and metastatic adenocarcinoma. In particular, hidradenomas whose digital involvement is extremely rare lack papillary projections and consist of two cell types: polygonal cells with eosinophilic cytoplasm and clear cells. p63 has been reported as a useful marker for distinguishing primary ADPC from metastatic adenocarcinomas. A predominantly solid pattern and focal or absent papillary structures may be a diagnostic pitfall in ADPC, particularly on small biopsy specimens.

Prognosis

Histopathologic features were not found to be predictive of outcome. The neoplasm tends to locally recur in up to 50 % of cases with an incomplete excision. The rate of metastasis is reported to range from 14 to 41 %, with both widespread metastasis and frequent metastasis to the lungs.

Treatment

Treatment with local therapy generally includes wide local excision or amputation, depending on the extent of involvement of the digit and bone. The usefulness of sentinel lymph node has not been defined. Local recurrence occurs in 48 % of patients between 2 months and up to 9 years after initial surgical excision. The local recurrence rate decreases to approximately 5 % with aggressive re-excision, but metastasis rates remain high at up to 14 % in all patients. Patients may also develop metastatic disease up to 20 years after initial presentation. The role of chemotherapy, radiotherapy, and targeted therapy with anti-epidermal growth factor receptor in metastatic ADPC remains unclear or under exploration.

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Porocarcinoma

25

Irina Margaritescu, Sara C. Shalin,
and A. Doru Chirita

Introduction

First described by Pinkus and Mehregan in 1963 as epidermotropic eccrine carcinoma, porocarcinoma (PC), the malignant counterpart of poroma, represents a very rare tumor derived from the dermal sweat gland duct and the acrosyringium.

Clinical Features

The tumor typically appears in the elderly, in the fifth to seventh decades of life. The average age at presentation is 69 years (range 8–91). Men and women are equally affected. The most common location is the lower extremity. Other common sites are the head and neck region, the trunk and the upper extremity. Occasionally, the tumor may appear on the genitals, lower and upper eyelid, ear, and the lip. The time interval between the appearance of the tumor and the diagnosis varies, but is rather large and ranges from several months to 50 years. Although most of the lesions appear de novo, they can also develop in a preexisting poroma or hidroacanthoma simplex in a significant proportion of cases. There are isolated reports of porocarcinoma arising in nevus sebaceus, linear epidermal nevus and seborrheic keratosis. The lesion may present as a slowly or rapidly growing nodule, a verrucous plaque, an ulcerated vegetating tumor, a pedunculated growth, or as a partly erosive multinodular plaque. It can have variable colors (erythematous, violaceous, brownish, or skin colored) and sizes (range 1–20 cm). Given its protean morphology, porocarcinoma can be mistaken for both benign and malignant neoplasms, such as a verruca vulgaris, seborrheic keratosis, poroma, pyogenic granuloma, angioma, basal cell carcinoma, Bowen's disease and squamous cell carcinoma, melanoma, atypical fibroxanthoma, and a cutaneous metastasis from visceral carcinoma (Fig. 25.1).

Pathology

At scanning magnification porocarcinoma may exhibit some similarities to a poroma such as the presence of anastomosing epithelial downgrowths with multiple foci of attachment to the

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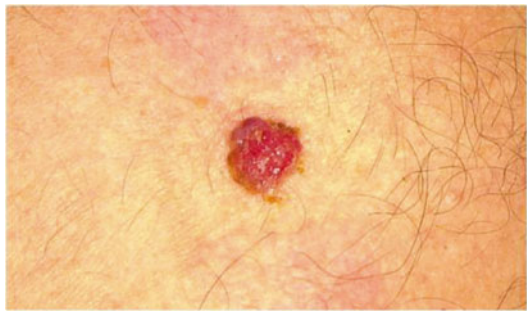

Fig. 25.1 Porocarcinoma. An exophytic reddish tumor on the anterior trunk of a 65-year-old man. It can easily be mistaken for a vascular tumor or an amelanotic melanoma (Courtesy of Cristian Tiglea, MD)

Fig. 25.2 A large and asymmetrical polypoid neoplasm exhibiting a broad pushing lower border with an infiltrative growth pattern in the deeper part

epidermis. However, the tumor has a silhouette of a malignant neoplasm, being large, asymmetrical, and poorly circumscribed and usually extending throughout the dermis and subcutaneous fat (Fig. 25.2). Some neoplasms have sharply delineated margins and a broad, pushing lower border, while others manifest an infiltrative growth pattern (Figs. 25.2 and 25.3). At higher magnification, the neoplasm exhibits two types of cells, basophilic poroid and cuticular with eosinophilic cytoplasm. Signs of ductal differentiation in the form of intracytoplasmic vacuoles and/or well-formed ducts lined by an eosinophilic cuticle are usually seen (Fig. 25.4). The cells have crowded, pleomorphic, and hyperchromatic nuclei, with many abnormal mitotic figures (Fig. 25.5). Intraepidermal spreading of tumoral cells can be seen in primary porocarcinomas, (Fig. 25.6) but is more prominent in metastatic lesions. Purely in situ cases also exist. Variants with clear cells, spindle cells, giant cells, and mucinous cells can sometimes be encountered. Some tumors may display colonization by dendritic melanocytes and melanin pigment accumulation into the cells. Areas with bowenoid changes may be found mainly in the superficial aspects of the neoplasms. Extensive squamous differentiation in the form of dyskeratotic cells and keratin whorls is a rare finding within the invasive component of the lesion. The neoplasm is embedded in a myxoid, vascular, or desmoplastic stroma. Comedo-like necrosis and cystic degeneration

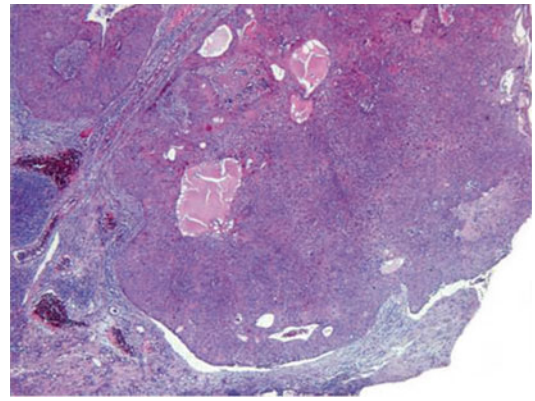

Fig. 25.3 Despite the presence of an artifactual cleft which imparts a superficial resemblance to a basal cell carcinoma, this neoplasm is composed of poroid and cuticular cells, and not of germinative ones

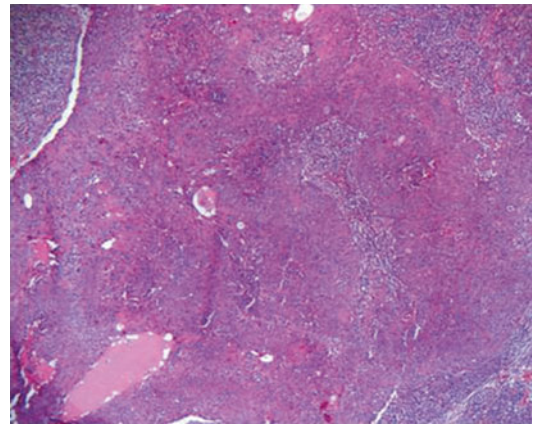

Fig. 25.4 The two types of cells characteristic of porocarcinoma, namely, poroid and cuticular, and signs of ductal differentiation can be easily identified

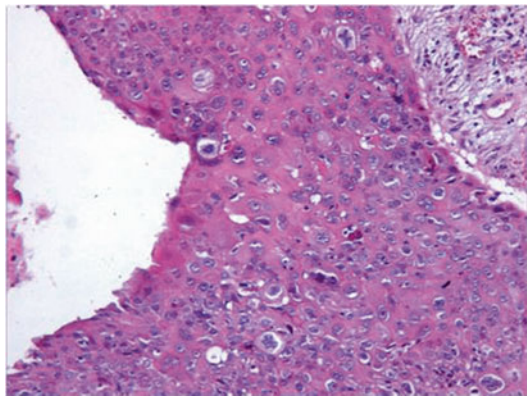

Fig. 25.5 The cells have crowded, pleomorphic, and hyperchromatic nuclei, with many abnormal mitotic figures

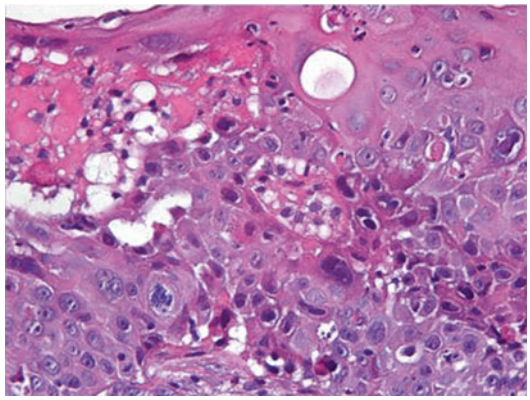

Fig. 25.6 The surface epidermis is replaced by abnormal tumoral cells

are other encountered features. Identification of lymphovascular invasion or perineural infiltration signifies a worse prognosis.

Histochemistry

Periodic acid-Schiff-positive with diastase digestible granules are present in the cytoplasm of the tumor cells. The ducts are also highlighted with diastase PAS stain. The cells are positive for amylophosphorylase and succinic dehydrogenase.

Immunohistochemistry

The tumoral cells stain variably with CEA, EMA, CAM5.2, BerEP4, CK15, and CK19, and they usually react strongly with CK7. CEA and EMA stains highlight the luminal structures.

Differential Diagnosis

The intraepidermal variant of porocarcinoma should be differentiated from clonal seborrheic keratosis, Bowen's disease, melanoma in situ, and Paget's disease. Unlike all these neoplasms, porocarcinoma usually displays at least some foci of ductal differentiation. Moreover, clonal seborrheic keratosis does not show atypia or mitosis, and Bowen's disease exhibits clear squamous differentiation, more pronounced keratinocyte atypia, and a disordered architecture. Paget's disease shows larger mucin-containing cells arranged as solitary units, nests, and glandular structures with apocrine differentiation. In melanoma in situ, the neoplastic cells always involve the dermoepidermal junction and characteristically stain with S-100 protein, MelanA, and HMB-45. The clear cell variant of porocarcinoma in situ should also be distinguished from sebaceous carcinoma which shows clear cells with bubbly cytoplasm due to lipid vacuoles. In addition, sebaceous carcinoma is not reactive with PAS and CEA stains. Invasive porocarcinoma should be differentiated from squamous cell carcinoma, basal cell carcinoma, Merkel cell carcinoma, and hidradenocarcinoma. Apart from the absence of ductal differentiation, squamous cell carcinoma shows more prominent nuclear pleomorphism and obvious squamous differentiation. An immunohistochemical panel which includes CEA, EMA, CAM5.2, CK7, CK15, CK19, BerEP4, and 34βE12 may be useful in the assessment of poorly

differentiated neoplasms. Basophilic cells in basal cell carcinoma are germinative and not poroid in nature and are arranged in a palisade at the periphery of the aggregations (Fig. 25.3). Even though Merkel cell carcinoma may show focal ductal differentiation, this tumor displays characteristic architectural and cytologic features that aid in the differential diagnosis. Moreover, Merkel cell carcinoma shows typical paranuclear dot-like keratin and CK20 positivity, and it is negative for CK7. Hidradenocarcinoma does not have a connection with the epidermis. Cutaneous metastases from visceral carcinomas can be excluded by a careful and detailed history coupled with a thorough clinical examination and imaging studies.

Prognosis

Porocarcinoma is a neoplasm with a potentially aggressive behavior. However, its prognosis seems difficult to assess due to the tumor's rarity and the rather short follow-up of most of the published cases. Based on the largest case series published to date (69 cases), the following parameters have been found to have prognostic significance, namely, number of mitoses (>14/HPF), lymphovascular invasion, and tumor depth (>7 mm). Tumors with an infiltrative rather than a pushing border and tumors with intraepidermal spread are particularly prone to local recurrence. Based on the same case series, approximately 1 out of 5 patients experience local recurrence and/or lymph node metastasis and 1 out of 10 patients experience distant metastasis or death. Mortality is much higher once the tumor has spread to the regional lymph nodes. Notably, Japanese authors have reported much higher lymph node metastases and mortality rates (1 out of 2 and 1 out of 3 patients, respectively).

Treatment

Complete surgical excision of the tumor with wide margins is the treatment of choice. Mohs micrographic surgery is recommended when dealing with tumors with infiltrative borders and intraepidermal spread. Sentinel lymph node biopsy may be of benefit for tumors with > 7 mm depth or high mitotic rate. Overall, chemotherapy and adjuvant radiotherapy have not proved to be effective for metastatic disease. Some benefits have been obtained with IFN-alpha, isotretinoin, and interleukin-2 alone or in combination with various chemotherapeutic agents (docetaxel, taxotere, tegafur).

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Primary Signet-Ring Cell/ Histiocytoid Carcinoma of the Eyelid

26

Franco Rongioletti

Introduction

Primary signet-ring cell/histiocytoid carcinoma of the eyelid is a very rare and locally aggressive neoplasm. The origin of the tumor, either eccrine or apocrine, is still a matter of debate, although some recent studies favor an apocrine differentiation. The tumors predominantly occur on the eyelids of middle-aged to elderly men (mean age = 67 years).

Clinical Features

The typical clinical presentation is a gradual swelling and thickening of the eyelid(s) (Fig. 26.1). The patient usually presents with an indurate lesion on one eyelid, especially the lower eyelid, with progressive extension to the other eyelid of the same affected side ("monocle-like" appearance). The delay time between the onset and diagnosis is up to 7 years as the clinical presentation mimics inflammatory process. Involvement of the axilla as a firm plaque or subcutaneous nodule has been reported.

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Pathology

Infiltrating cords of rectangular, cuboidal, or polyhedral tumor cells forming "single-file pattern" are present throughout the dermis (Fig. 26.2). Loosely cohesive infiltrating sheets are also noted. Most of the tumor cells have an abundant eosinophilic or amphophilic cytoplasm with intracytoplasmic vacuoles resembling histiocytes (Fig. 26.3). A small number of cells exhibit a signet-ring appearance (Fig. 26.4). The nuclei are round with finely granular nuclear chromatin and distinct nucleoli. Mitoses can be found. Periodic acid–Schiff positive highlights intracytoplasmic vacuoles. There is little or absent gland formation. The tumor cells showed positive immunoreactivity to a panel of cytokeratins (CAM 5.2, CK7, AE1/3, 34BE12, and MNF116), gross cystic disease fluid protein-15 (GCDFP-15), carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), CD15, and Ber-EP4 (Fig. 26.5). Staining for CK20, CDX-2, p63, D2-40, and estrogen receptor (ER) is negative. However, some cases in the literature are stained positively by estrogen receptors and progesterone receptors.

Differential Diagnosis

The definite diagnosis is made by exclusion of cutaneous metastases to the eyelid from carcinomas of other primary sites especially the histiocytoid and lobular variants of breast

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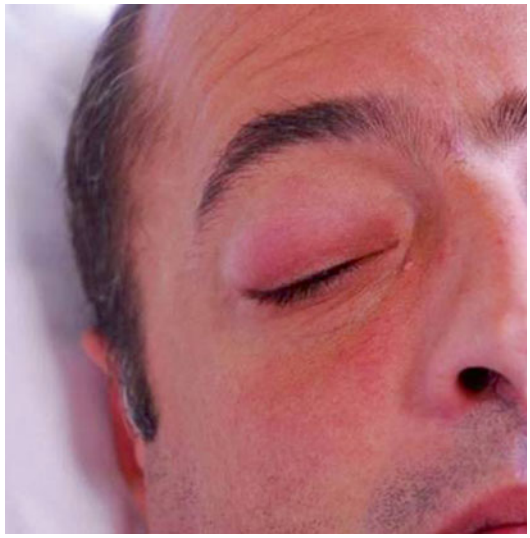

Fig. 26.1 The patient presents with a gradual chronic swelling and thickening of the upper eyelid

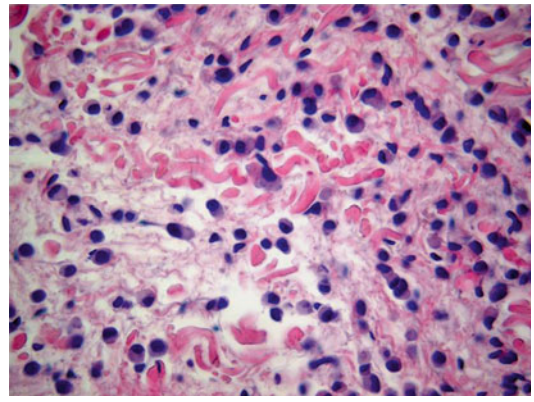

Fig. 26.3 Most of the tumor cells have an abundant amphophilic cytoplasm

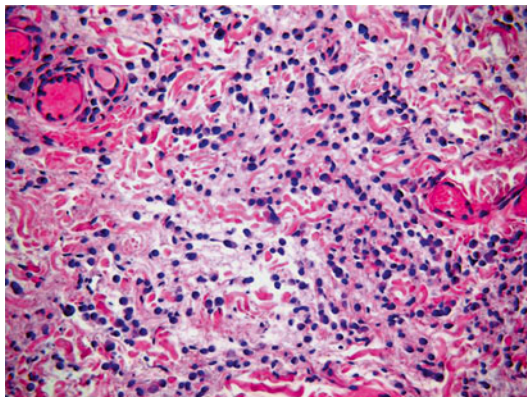

Fig. 26.2 Infiltrating cords of rectangular, cuboidal, or polyhedral tumor cells forming "single-file pattern" are present throughout the dermis. There is little or absent gland formation Courtesy C.Tomasini,Turin,Italy

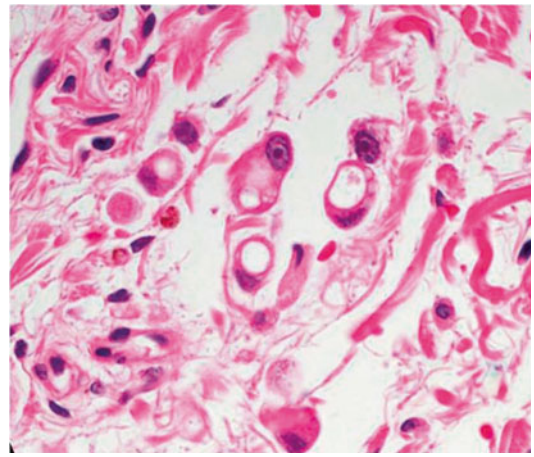

Fig. 26.4 A small number of cells exhibit a signet-ring appearance

carcinoma and gastrointestinal tract carcinoma. Moreover, the clinical presentation mimics inflammatory process such as orbital cellulitis, chalazion, and blepharoconjunctivitis.

Prognosis

The neoplasm follows an indolent course with slow and painless growth and high rate of recurrences that are related to incomplete tumor removal or orbital involvement. The recurrence-free period ranges from 5 months to 8 years. Metastasis occurs in up to half of patients, especially to the regional lymph nodes.

Treatment

Treatment modalities include surgery (excision with wide margins or orbit exenteration) and radiotherapy with or without adjuvant chemo-

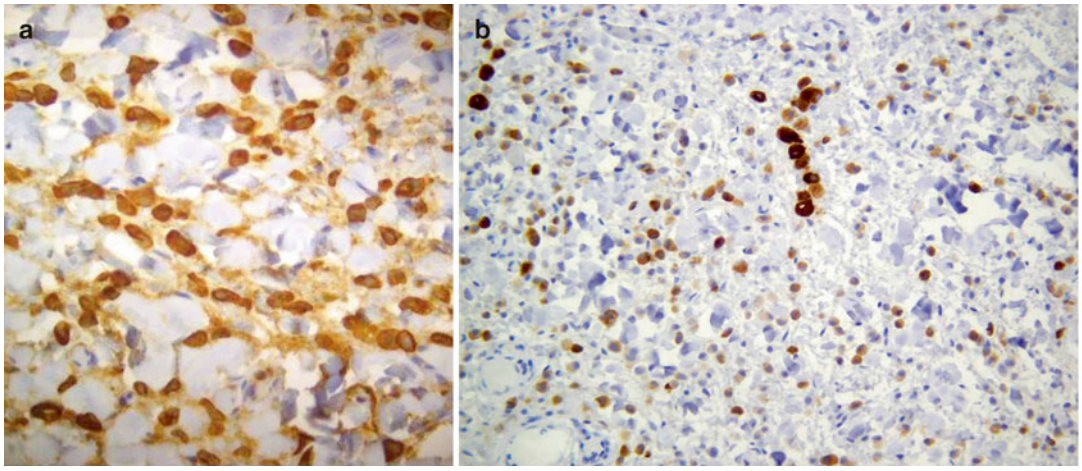

Fig. 26.5 (**a**). The tumor cells showed positive immunoreactivity to cytokeratins (AE1/3) and (**b**) gross cystic disease fluid protein-15 (GCDFP-15)

therapy (5-fluorouracil) or antiestrogen treatment. Mohs surgery merits to be considered, while the role of sentinel lymph node biopsy deserves further studies. Radiotherapy alone has been proposed for old patients with extensive adnexal or orbital infiltration.

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Primary Mucinous Carcinoma of the Skin

27

Elisa Cinotti and Franco Rongioletti

Introduction

Primary mucinous carcinoma of the skin (PMCS) is a rare adnexal tumor that rarely metastasizes and is associated with low mortality. Although it is considered to be derived from the deepest portion of the eccrine sweat duct, its eccrine or apocrine origin is still a matter of controversy. The first description dates back to 1952 and was later refined by Mendoza and Helwig in 1971. Actually, fewer than 150 cases have been reported in the English literature.

Clinical Features

PMCS is rare with an incidence of less than 0.1 per million and about one case in every 150,000 specimens of cutaneous lesions. It most frequently occurs between the ages of 50 and 70 and has a male predominance of 2:1. The tumor usually presents as a slow-growing, asymptomatic, flesh-colored, or erythematous nodule with a slightly translucent surface due to distention of the overlying skin. There have been isolated reports of ulceration, blue color, and telangiectasias. The eyelid is the most commonly affected site (41 %), followed by the scalp (17 %), face (14 %), axilla (9 %), chest/abdomen (7 %), vulva (4 %), neck (2 %), extremity (2 %), canthus (2 %), groin (1 %), and ear (1 %).

Pathology

PMCS is a well-limited dermal tumor consisting of small islands of epithelial tumor cells "floating" in large pools of slightly basophilic mucin separated by thin fibrovascular septa (Figs. 27.1 and 27.2). The clustered epithelial cells are small and uniform with cuboidal nuclei and can form ductal structures. Branching and cribriform patterns are also seen. Mitoses are uncommon. The mucin is periodic acid–Schiff positive and stains with colloidal iron, mucicarmine, and Alcian blue at pH 2.4. The mucin is classified as a sialomucin, a nonsulfated mucopolysaccharide that is hyaluronidase and diastase-resistant and sialidase labile.

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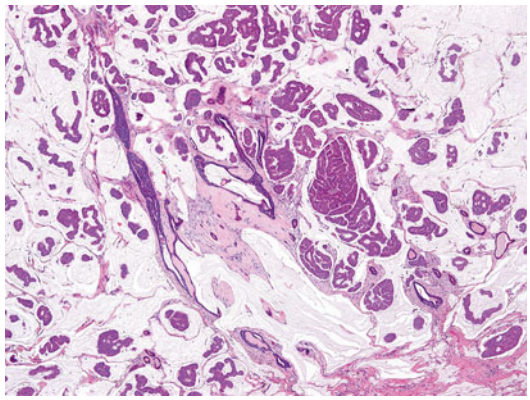

Fig. 27.1 Primary mucinous carcinoma of the skin. A dermal tumor consisting of small islands of epithelial tumor cells "floating" in large pools of slightly basophilic mucin separated by thin fibrovascular septa (Courtesy of D. Kazakov, Pilsen, Czech Republic)

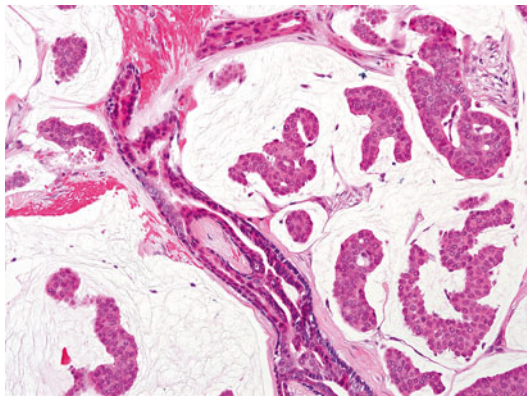

Fig. 27.2 Primary mucinous carcinoma of the skin. The clustered epithelial cells are small and uniform with cuboidal nuclei and can form ductal structures in the epithelial islands floating in large pool of mucin (Courtesy of D. Kazakov, Pilsen, Czech Republic)

Differential Diagnosis

The clinical differential diagnosis is broad and includes other adnexal tumors, basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma, and epidermoid cyst. Histological differential diagnosis includes metastatic adenocarcinomas, particularly of the breast and gastrointestinal tract, mucinous basal cell carcinomas, and other sweat gland carcinomas. The mucin in other sweat gland carcinomas is usually a sulfated mucopolysaccharide with different staining properties. Metastatic mucinous adenocarcinoma may be histologically indistinguishable from PMCS. A few subtle histological features should be searched for and may provide help in establishing the correct diagnosis: mucinous carcinomas have more mucin, more clusters of epithelial cells, fewer ductal structures, fewer solid areas, and fewer mitoses than metastatic tumors. An additional clue for a primary lesion is the presence of an in situ component identified as epithelial islands being bounded by a myoepithelial layer, which is highlighted by p63, CK 5/6, calponin, SMA, and HHF-35. Immunohistochemical staining and cytokeratin profiles are also of great help in the differential diagnosis. PMCS shows positive cytoplasmic staining with S-100, carcinoembryonic antigen (CEA), vimentin, epithelial membrane antigen (EMA), α-actin, and cytokeratin 7 (CK7), as well as with estrogen receptor and progesterone receptor. CK20 is useful to differentiate metastatic lesions from the intestinal tract since it is negative in PMCS. In addition, "dirty necrosis" is frequently found in intestinal mucinous adenocarcinomas involving the skin. In mammary mucinous adenocarcinoma involving the skin, lesions are on the chest wall, breast, and axilla, and these locations can serve as clue to the breast origin.

Prognosis

After excision, mucinous carcinoma has a high rate of local recurrence (30 %), probably related to its special location (eyelid and deep dermis). Local metastases to regional lymph nodes have been reported in 10 % of cases, whereas distant metastases are rare. The low metastatic potential has been linked to the avascular characteristic of the tumor.

Treatment

Early wide surgical excision of the tumor with at least 1 cm margin is the treatment of choice. Mohs micrographic surgery can be an alternative

to wide local excision. Radiotherapy and chemotherapy are not effective. Because of the histological and immunohistochemical overlap with some metastatic neoplasms, a workup to rule out metastatic lesions should be completed in these patients.

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Endocrine Mucin-Producing Sweat Gland Carcinoma

28

Franco Rongioletti

Introduction

Endocrine mucin-producing sweat gland carcinoma (EMPSGC), first described in 1997, is a low-grade sweat gland tumor characterized by neuroendocrine differentiation; solid, cystic, and papillary architecture; and tendency to occur on the eyelid. It is considered histologically analogous to endocrine ductal carcinoma/solid papillary carcinoma of the breast. Only 20 cases have been reported so far.

Clinical Features

The tumor typically presents as a slow-growing, skin-colored, poorly circumscribed, and solid or partially cystic nodule affecting elderly women almost thrice as often as men. Patients' ages ranged from 48 to 84 years, with a mean of 70.5 years. The eyelids are the typical site of involvement

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Pathology

Multiple solid lobules showing areas of cribriform and intracystic papillary architecture are seen in the dermis (Fig. 28.1). The tumor islands often resemble an intraductal carcinoma with malignant cells expanding preexisting duct-like structures. Cytologically, the lobules are made by oval, small- to medium-sized cells with neuroendocrine differentiation, moderate degrees of nuclear pleomorphism with scattered mitotic figures, and intracellular and extracellular mucin production. An Alcian blue–periodic acid-Schiff stain revealed intracytoplasmic and luminal mucin throughout the tumor that is never abundant in contrast to mucinous adenocarcinoma of the skin. However, most patients have coexisting invasive mucinous carcinoma, which might suggest that EMPSGC is a precursor of invasive mucinous carcinoma of the skin.

To diagnose EMPSGC, the expression of specific neuroendocrine markers such as chromogranin or synaptophysin is required (Fig. 28.2). Furthermore, the tumor cells are positive for neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), CK7, gross cystic disease fluid protein (GCDFP-15), and the estrogen, progesterone, and androgen receptors. The demonstration of a peripheral layer of myoepithelial cells with calponin, p63, and CD10 plays in favor of an in situ rather than invasive carcinoma, while lack of identification of individual myoepithelial cells supports the invasive nature of the tumor.

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Differential Diagnosis

The immunohistochemical profile along with the histological resemblance to breast carcinoma makes it crucial to rule out the possibility of cutaneous metastases in all cases. Moreover, EMPSGC should be differentiated from other adnexal neoplasms like hidradenoma, hidradenocarcinoma, apocrine adenoma, and dermal duct tumor. Given its basaloid nature, EMPSGC may also be confused with an unusual nodular basal cell carcinoma. Positive staining with neuroendocrine markers can conclusively distinguish EMPS from similar adnexal neoplasms.

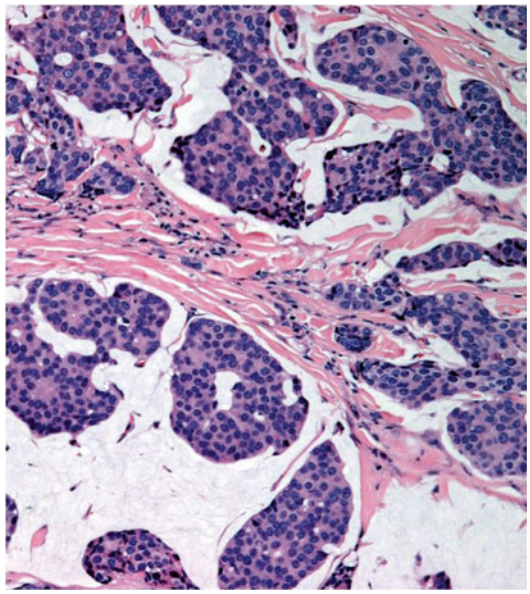

Fig. 28.1 Endocrine mucin-producing sweat gland carcinoma. Multiple solid lobules showing areas of cribriform architecture, duct-like structures, and extracellular mucin production

Prognosis

The overall prognosis of EMPSGC is good. However, the association of EMPSGC with an invasive mucinous adenocarcinoma makes the prognosis a little bit worse. The tumor may recur but distant metastases have not been reported. The recurrence seems to be related to technical difficulties and cosmetic concerns related to surgery involving the eyelid region.

Treatment

While the treatment of EMPSGC consist of a complete surgical excision with a margin *of* at least 5 mm or more. Mohs micrographic surgery has been reported to be an appropriate line of management.

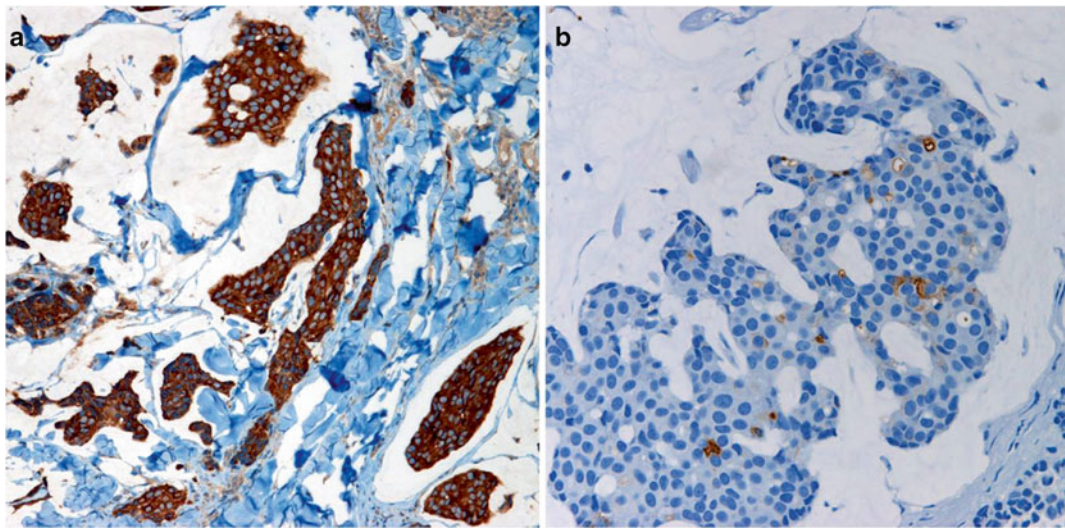

Fig. 28.2 (**a**). The tumor cells are strongly positive for synaptophysin and (**b**) focally for chromogranin

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Part V

Tumours of Fibrous and Myofibroblastic Tissue

Low-Grade Fibromyxoid Sarcoma

29

Elisa Cinotti, Catherine Douchet,
and Franco Rongioletti

Introduction

Low-grade fibromyxoid sarcoma (LGFMS) is an uncommon deep soft tissue neoplasm first described by Evans in 1987 as "a metastasizing soft tissue tumour with a deceptively benign histological appearance." Since then, about 500 cases have been reported in the literature.

Clinical Features

It mostly occurs as a nodule or mass in the deep and subcutaneous soft tissue of the lower limbs and groin, followed by the trunk wall, internal organs, upper limbs, head and neck, shoulders, and axillae. Both sexes are similarly involved. The tumor mostly affects the young and middle-aged adults and is rare in infants.

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Pathology

It is characterized by its relatively benign histological appearance with spindle and stellate-shaped cells, in a whorled or linear arrangement, and with collagenized and myxoid areas (Figs. 29.1 and 29.2). The cells have a pale eosinophilic cytoplasm, uniform round to ovoid nuclei, and absent to indistinct nucleoli. They have a deceptively benign appearance, with no or slight nuclear pleomorphism and few mitotic figures (Fig. 29.3). Necrosis is generally absent. Most of the tumors are well circumscribed but not encapsulated.

Some recurrences and metastases have demonstrated zones of increased cellularity and somewhat increased mitotic activity. However, such areas have typically regular cells without pleomorphism.

Neoplastic cells stain with vimentin and show variable focal positivity for muscle-specific actin; smooth muscle actin, desmin, and calponin; and CD34, while they are negative for S-100 protein, nuclear β-catenin, h-caldesmon, CD31, Leu-7, neuron-specific, cytokeratin, and epithelial membrane antigen. Recently, MUC4, a transmembrane glycoprotein that functions in cell growth signaling pathways, has been reported as a highly sensitive and specific immunohistochemical marker for LGFMS. Moreover, 90 % of LGFMS exhibit the t(7;16)(q34;p11) translocation encoding a FUS/CREB3L2 fusion oncoprotein. Less frequently, FUS/CREB3L1 fusion oncoprotein is expressed.

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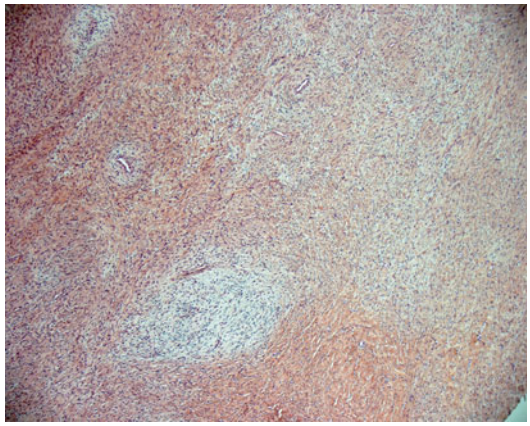

Fig. 29.1 Low-grade fibromyxoid sarcoma. Histological appearance with spindle and stellate-shaped cells, in a whorled or linear arrangement, and with collagenized and myxoid areas

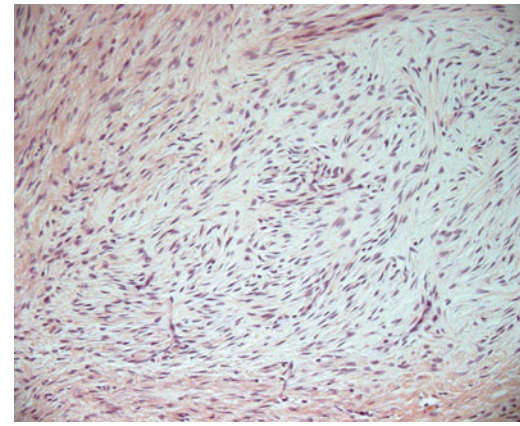

Fig. 29.3 Low-grade fibromyxoid sarcoma. The spindle cells have a deceptively benign appearance, with no or slight nuclear pleomorphism

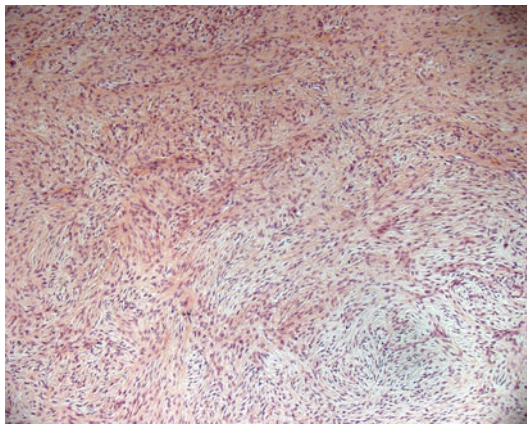

Fig. 29.2 Low-grade fibromyxoid sarcoma. Collagenized and myxoid areas with spindle cell proliferation

Differential Diagnosis

The differential diagnosis encompasses a number of entities characterized by spindle cell proliferations with myxoid morphologies. Being LGFMS a low-grade tumor, it can mimic both malignant and benign entities. Regarding soft tissue tumors, the main differential diagnosis includes low-grade myxofibrosarcoma, myxoid neurofibroma, peripheral nerve sheath tumor, schwannoma, myxoid solitary fibrous tumor, desmoid fibromatosis, epithelioid sarcoma, sclerosing epithelioid fibrosarcoma, superficial angiomyxoma, superficial acral fibromyxoma, and acral myxoinflammatory fibroblastic sarcoma.

Low-grade myxofibrosarcoma typically has more uniform myxoid stroma, with less swirling of tumor cells and more cellular atypia. Myxoid neurofibroma has more slender wavy nuclei and consistently shows S-100 positivity. Peripheral nerve sheath tumor may show fibrous and myxoid areas and typically show diffuse staining for epithelial membrane antigen, whereas LGFMS may show only rare focal positivity. Schwannomas are S-100 positive. Myxoid solitary fibrous tumor is uniformly immunoreactive for CD34. Although deep fibromatosis usually has a more fascicular architecture, there can be similarities with LGFMS, and immunohistochemical staining for nuclear catenin can distinguish deep fibromatosis from LGFMS.

Occasional cases of LGFMS show areas indistinguishable from sclerosing epithelioid fibrosarcoma; moreover, some cases of sclerosing epithelioid fibrosarcoma show morphological and molecular overlap with LGFMS. Hyalinizing spindle cell tumor with giant rosettes, characterized by focal presence of collagen rosettes, consisting of a central core of hyalinized collagen

surrounded by a cuff of epithelioid fibroblasts, shares the same cytogenetic abnormality of LGFMS, the FUS/CREB3L2 fusion gene, and can be considered a morphological variant of LGFMS.

Prognosis

In spite of the low-grade and benign histological appearance, LGFMS has a high rate of recurrence. Metastases are rare and are mainly located in the lung or occasionally in the soft tissues and the bone. Death from metastasis is even rarer and mainly occurs if metastases cannot be excised.

Treatment

Surgical excision of the tumor and of possible metastases is the treatment of choice. Due to the low grade of malignancy and therefore the low mitotic rate, LGFMS is not very chemo- or radiosensitive. Because of the relative high rate of recurrence and distant metastasis, longtime follow-up is advised.

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Myxofibrosarcoma

30

Elisa Cinotti and Franco Rongioletti

Introduction

Myxofibrosarcoma (MFS) is a myxoid variant of the malignant fibrous histiocytoma. The tumor does not demonstrate histiocytic differentiation, and consequently the designation MFS, which emphasizes the fibroblastic nature and abundant myxoid stroma, is now preferred to "myxoid malignant fibrous histiocytoma."

Clinical Features

It usually involves the deep soft tissues and striated muscles of the proximal part of the extremities. Up to half of cases may arise in the subcutaneous tissues, although less than 10 % are confined to the subcutis without underlying deeper involvement. When concerning the subcutaneous tissue, it usually presents as a gradually enlarging painless mass with a tendency for diffusely infiltrative growth, which may extend to the overlying dermis (Fig. 30.1). It is one of the most common fibroblastic sarcomas in older patients and tends to affect patients in the sixth to eighth decades. However, the overall age range is wide, and some cases have been reported in patients as young as 15 years. It has no significant gender predilection.

Pathology

MFS presenting in the skin involves the reticular dermis, although the main bulk of the tumor is located in the subcutaneous tissue (Fig. 30.1). Superficial portions of MFS often appear benign, while deeper regions contain more obvious histomorphologic evidence of malignancy. Consequently, superficial cutaneous biopsies may result in an underestimation of tumor grade or even misdiagnosis as a benign process.

MFS is usually multinodular with ill-defined, deceptively infiltrative margins (macroscopically and microscopically) that extend into surrounding tissues, resulting in distant microscopic tumor deposits that predispose to local recurrence after resection.

MFS is characterized by a proliferation of fusiform or stellate fibroblasts and delicate, thin-walled curvilinear blood vessels set within a prominent hyaluronic acid-rich myxoid stroma (Fig. 30.2). A prominent mixed inflammatory infiltrate may be seen (Fig. 30.3). It may exhibit a

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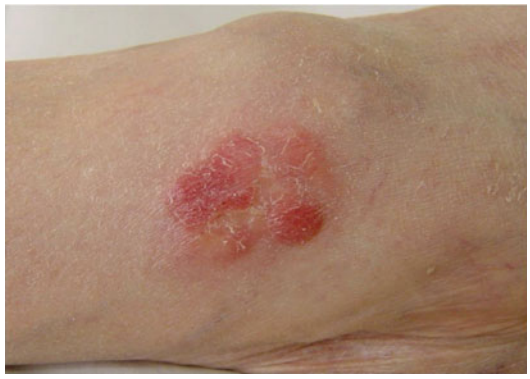

Fig. 30.1 Myxofibrosarcoma presenting with a gradually enlarging painless mass with erythema and a tendency for diffusely infiltrative growth on the leg

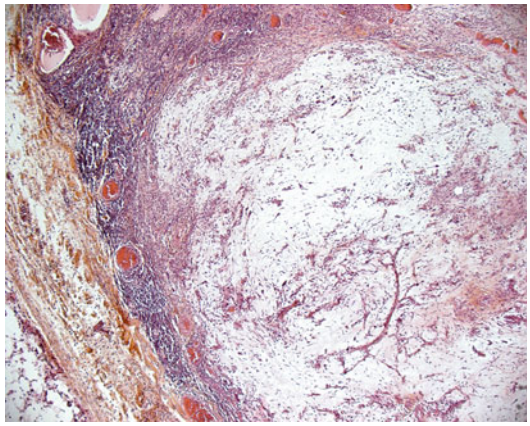

Fig. 30.2 Myxofibrosarcoma presenting in the skin involves the reticular dermis, although the main bulk of the tumor is located in the subcutaneous tissue

remarkably broad spectrum of histopathologic features ranging from low to high grade. Low-grade myxofibrosarcomas are hypocellular tumors, composed of relatively monomorphous cells. Careful examination invariably shows nuclear pleomorphism and hyperchromasia, but mitotic figures and other overtly malignant features may be inconspicuous (ca. 2 per 10 high-power field) in low-grade lesions (Fig. 30.4). It may contain cells resembling lipoblasts, sometimes referred to as pseudolipoblasts. This tumor cell subtype is filled with bubbly cytoplasmic vacuoles that compress and indent the nuclei in a manner similar to that seen in the lipoblasts that characterize liposarcomas. These cells are actually fibroblasts, and their vacuoles contain acidic glycosaminoglycans rather than the lipids of lipoblasts. Pseudolipoblasts may be a helpful diagnostic clue, but they are not invariably present, and several other tumors may produce morphologically similar cells.

With increasing histological grade, myxofibrosarcomas show increasing cellularity, nuclear pleomorphism, and mitotic activity. Hemorrhage and necrosis can be present. Cells are usually spindle or ovoid but may also exhibit predominantly epithelioid cytologic features.

Immunohistochemically, tumoral cells are positive for vimentin and negative for desmin, pancytokeratin, CD31, CD34, CD68, and HMB45. S-100 can be positive in focal areas. In a minority

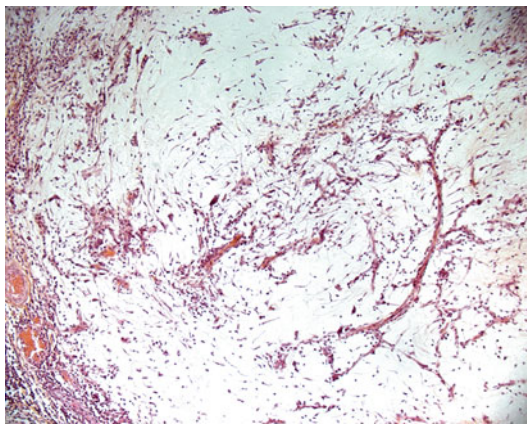

Fig. 30.3 Myxofibrosarcoma is characterized by a proliferation of fusiform or stellate fibroblasts and delicate, thin-walled curvilinear blood vessels set within a prominent hyaluronic acid-rich myxoid stroma

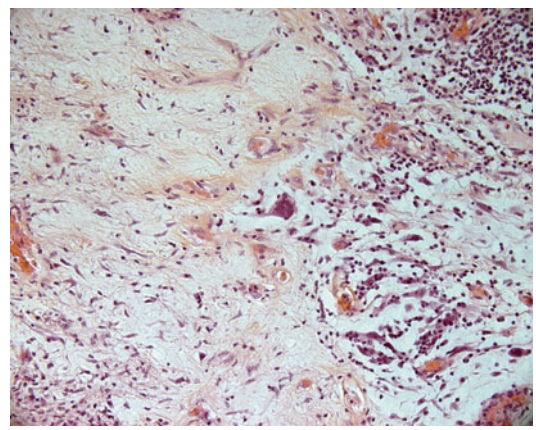

Fig. 30.4 An infiltrate of atypical spindle cells within a prominent myxoid stroma and a pleomorphic multinucleated epithelioid cell component associated with a mixed inflammatory infiltrate may be seen

of cases, some spindled or larger eosinophilic tumor cells express smooth muscle actin (SMA) and/or muscle-specific actin (MSA), suggestive of focal myofibroblastic differentiation. The myxoid matrix is composed of polysaccharide glycosaminoglycans such as hyaluronic acid, chondroitin sulfate, and keratan sulfate that stain positively with Alcian blue and not at all or very weakly with the periodic acid–Schiff (PAS) stain.

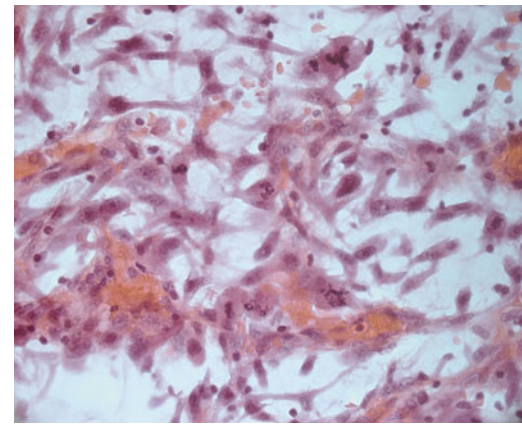

Fig. 30.5 The infiltrate shows nuclear pleomorphism and hyperchromasia with rare mitotic figures

Differential Diagnosis

The histopathologic differential diagnosis includes both benign and malignant entities. Particularly, if only superficial portions are examined, it can be very difficult to exclude benign myxoid fibroblastic lesions such as superficial angiomyxoma (cutaneous myxoma), myxoid nodular fasciitis, nerve sheath myxoma, myxoid neurofibroma, myxoid pleomorphic fibroma, and papular mucinosis. Cytologic atypia, nuclear hyperchromasia, curvilinear blood vessels, and subcutaneous infiltration should be searched to diagnose MFS. Superficial angiomyxoma has often a mixed inflammatory infiltrate in the stroma, rare mitotic figures, and no cellular atypias (Fig. 30.5). Moreover, differently from MFS, it is MSA and SMA negative and CD34 positive. Myxoid nodular fasciitis is well demarcated and has inflammatory infiltrate, erythrocyte extravasation, and fascicular organization that are usually absent in MFS. Nerve sheath myxoma typically occurs in younger patients, is well demarcated, and is strongly immunoreactive for S-100 protein. The absence of S-100 reactivity also essentially excludes myxoid neurofibroma.

Myxoid lipoma can be distinguished by the absence of adipocytic differentiation in MFS, but it may be difficult to distinguish tumoral adipocytes from normal fat entrapped by tumor. Moreover, myxoid lipoma is CD34 positive.

Low-grade tumors that should be differentiated from MFS are pleomorphic hyalinizing angiectatic tumor (PHAT), low-grade fibromyxoid sarcoma (LGFMS), myxoid dermatofibrosarcoma protuberans (DFSP), and inflammatory fibrosarcoma. PHAT is a low-grade neoplasm that can be distinguished from MFS by the presence of atypical stromal cells containing hemosiderin, partially thrombosed ectatic vessels, and possibly an inflammatory infiltrate. Because of similarity of names, LGFMS is confused with MFS. However, clinically LGFMS occurs in young adults while MFS occurs in elderly patients, and histologically LGFMS has whorled aggregates of spindle cells, fibrous stroma alternating with myxoid stroma, and abrupt transition from fibrous to myxoid stroma, features that are usually absent in MFS. In addition, it lacks prominent thin-walled curvilinear vasculature structures and pseudolipoblasts. A confirmation of LGFMS can be achieved by the demonstration of the FUS/CREB3L2 fusion gene. Myxoid DFSP generally lacks the multilobular growth pattern, curvilinear vessels, and cytologic atypia encountered in MFS and presents a storiform architecture. Inflammatory fibrosarcomas are acral and have a prominent inflammatory infiltrate and atypical cells with large eosinophilic nuclei.

In intermediate- and high-grade MFS, the differential diagnoses are high-grade malignancies including spindle cell and myxoid melanoma, myxoid liposarcoma, extraskeletal myxoid chondrosarcoma, myxoid leiomyosarcoma, spindle cell squamous carcinoma, and malignant myxoid peripheral nerve sheath tumor. S-100 protein is expressed by myxoid melanoma and by a group of myxoid liposarcoma (40 %), extraskeletal

myxoid chondrosarcoma (20 %), and malignant myxoid peripheral nerve sheath tumor (<50 %). Liposarcoma has indented nuclei, cytoplasmic vacuoli, and an arborizing vascular pattern, rather than a curvilinear capillary pattern. Extraskeletal myxoid chondrosarcoma is well demarcated and presents a multinodular architecture defined by fibrous septa that divide the tumor into hypocellular lobules with myxoid matrix. Leiomyosarcoma is identified by SMA and MSA positivity in most cases and the ultrastructural presence of cytoplasmic dense bodies, marginal dense plaques, and myofilaments. The lack of epithelial differentiation excludes a carcinoma. Malignant myxoid peripheral nerve sheath tumor often exhibits a more organized fascicular architecture and is usually situated within the deep soft tissue adjacent to large nerves.

Prognosis

The prognosis depends upon the histological grade of the initial lesion, as well as the size. The low-grade end of the spectrum is characterized by indolent biological behavior with local recurrence but no metastases, while high-grade lesions are associated with a 30–50 % risk of metastasis. Fanburg-Smith et al. reported a higher infiltrative potential of MFS in the subcutaneous tissue in contrast to the intramuscular tumors, leading to a higher risk of local recurrence. Tumors tend to recur, often in relation to incomplete resection, and there is a tendency for histological and biological progression in local recurrences, which then increases the risk of metastasis.

Metastasis occurs in a significant number of high-grade tumors. The lung and bone are favored metastatic sites, but spread to regional lymph nodes may also occur. The overall 5-year survival rate is 60–70 %.

Treatment

Wide excision followed by radiotherapy is the first-choice treatment.

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Fibrosarcoma

31

Elisa Cinotti, Catherine Douchet,
and Franco Rongioletti

Introduction

Fibrosarcoma is a malignant tumor of fibroblasts that shows no evidence of other cellular differentiation. In the past, any sarcoma with fibroblasts was termed fibrosarcoma and represented two thirds of all sarcomas. In the last two decades, the diagnosis of fibrosarcoma has become much more rare, with better ways of studying tissue such as immunohistochemistry and cytogenetics. Many of these tumors have been called "MFH," which itself has been renamed "Undifferentiated pleomorphic sarcoma (UPS)" in the soft tissue classification of the World Health Organization (WHO) of 2002.

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Clinical Features

Fibrosarcoma is primarily a tumor of the deep soft tissues that only rarely develops in the skin and superficial subcutis. Unfortunately, there are no distinct clinical characteristics of fibrosarcoma. Fibrosarcoma can be part of the spectrum of thermal burns-induced, radiation-induced, or radiation-associated sarcomas, representing about 15 % of the histological subtypes associated to radiation. Cutaneous fibrosarcoma may also result from extension of a tumor arising in deeper tissues. Fibrosarcoma is a rare diagnosis compared to other sarcoma subtypes. No difference between the sexes has been noted. The tumor affects predominantly persons aged 30–55 years, although there is an uncommon clinical subset involving neonates and young children (congenital-infantile fibrosarcoma). This variant accounts for 20–50 % of malignant soft tissue tumors in infants and neonates. Approximately 70 % develops on the extremities, with the remaining 30 % occurring on the head and neck. Axial lesions are uncommon. The lesions may be highly vascular and masquerade clinically as a hemangioma.

Pathology

The tumor is characterized by relatively monomorphic elongated, spindle cells that grow in interlacing fascicles, forming a so-called herringbone pattern (Fig. 31.1). Storiform areas can

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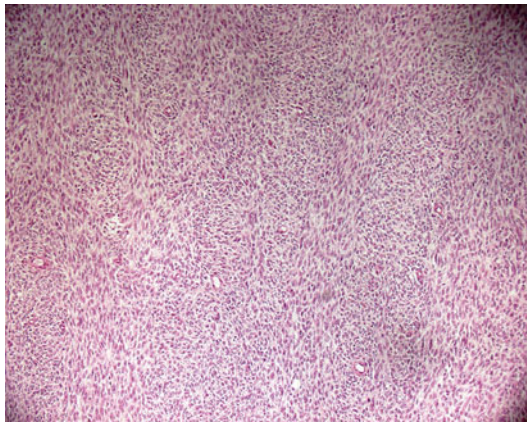

Fig. 31.1 Fibrosarcoma. The tumor is composed of monomorphic elongated, spindle cells that grow in interlacing fascicles, forming a so-called herringbone pattern

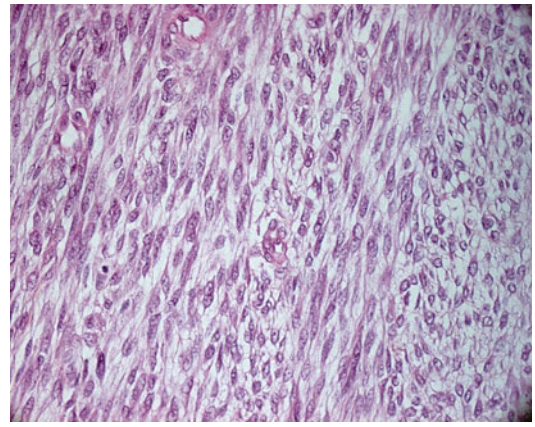

Fig. 31.3 Fibrosarcoma. The cells have tapered, dark nuclei with variably prominent nucleoli and scanty cytoplasm. Mitotic figures are present

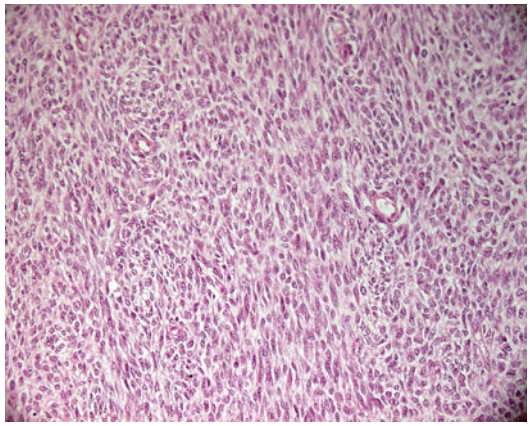

Fig. 31.2 Fibrosarcoma. Herringbone pattern

occasionally be present. Well-differentiated fibrosarcomas are rich in mature collagen between the individual cells. The cells have tapered, dark nuclei with variably prominent nucleoli and scanty cytoplasm. Mitoses are common (Figs. 31.2 and 31.3). Tumors showing a greater degree of pleomorphism are better classified as undifferentiated pleomorphic sarcoma.

Fibrosarcoma occasionally shows limited expression of SMA, representing myofibroblastic differentiation. CD34-positive tumors with fibrosarcoma morphology probably represent fibrosarcoma arising in a dermatofibrosarcoma protuberans or fibrosarcoma-like progression in solitary fibrous tumor.

The *congenital-infantile* variant is usually more cellular and composed of smaller cells with prominent mitotic activity. Foci of necrosis may be present. Unlike the adult variant, the interlacing fascicular (herringbone) pattern is not always seen.

The tumor cells express vimentin, but not always desmin, S100 protein, or smooth muscle actin. Recently, a novel chromosomal translocation t(12;15)(p13;q25) has been identified in the congenital-infantile group, giving rise to an *ETV6–NTRK3* fusion gene.

Differential Diagnosis

Fibrosarcoma is a diagnosis of exclusion, once the possibility of other spindle cells tumors such as low-grade fibromyxoid sarcoma (and its variants hyalinizing spindle cell tumor with giant rosettes), myxofibrosarcoma, dermatofibrosarcoma protuberans, desmoid tumor, synovial sarcoma, malignant peripheral nerve sheath tumor, spindle cell melanoma, and spindle cell squamous carcinoma have been ruled out.

Sclerosing epithelioid fibrosarcoma (SEF) and the inflammatory fibrosarcoma are distinct entities from fibrosarcoma. SEF is a low-grade sarcoma and is composed of small- to medium-sized epithelioid cells with a clear or pale cytoplasm, arranged in cords and strands, and embedded in a

fibrotic and hyalinized stroma. A subset of SEF appears to be related to low-grade fibromyxoid sarcoma. Inflammatory fibrosarcoma is synonymous to inflammatory myofibroblastic tumor or acral myxoinflammatory fibroblastic sarcoma. Inflammatory fibrosarcoma is composed of fibroblastic and myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and/or eosinophils.

Prognosis

Prognosis depends on the size, histological grade, and depth (superficial or deep). Congenital-infantile *fibrosarcoma* is much less aggressive than adult-type fibrosarcoma despite a similar histological appearance. Recurrences are frequent and metastases, when present, are usually located in the lungs and bone and rare in lymph nodes.

Treatment

Surgical resection remains the mainstay of curative therapy. Adjuvant radiotherapy is often used when the tumor measures more than 5 cm in size. The use of adjuvant chemotherapy remains controversial. In metastatic cases, possible chemotherapies are doxorubicin, ifosfamide or dacarbazine.

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Dermatofibrosarcoma Protuberans 32

Irina Margaritescu and A. Doru Chirita

Introduction

Dermatofibrosarcoma protuberans (DFSP), first described clinically by Darier and Ferrand in 1924 and histopathologically by Taylor and Helwig in 1962, represents a rare low-grade malignancy with a tendency for local recurrence and minimal capacity to produce distant metastasis. Its pathogenesis and histogenesis are not completely known. DFSP has been reported to arise at the site of previous radiotherapy or trauma, in burn scars, and in surgical and immunization sites. Over the years, different lines of differentiation for DFSP have been proposed: fibroblastic, histiocytic, and neural. It has also been suggested that DFSP may originate from an undifferentiated mesenchymal cell. The majority of tumors have a reciprocal translocation, t(17; 22)(q22; q13), or a supernumerary ring chromosome composed of hybrid material derived from t(17; 22). This translocation fuses the gene for platelet-derived growth factor B chain (PDGFB) on chromosome 22 with the collagen 1 alpha 1 (COL1A1) gene on chromosome 17. The fusion protein COL1A1–PDGFB is set up to produce fully functional PDGFB (a tyrosine kinase that acts as a growth factor for connective tissue cells), which is thought to cause DFSP tumor formation.

Clinical Features

DFSP most commonly appears in young adults between 20 and 39 years of age, but it may occur at any age, from the newborn to elderly. There is an almost equal sex distribution, with only a slight male predominance. The most common location is the trunk, which accounts for almost half of all cases, followed by the proximal extremities and the head and neck region. Uncommonly, it can appear on the hands and feet and exceptionally on the genital and oral mucosa. Usually, the lesion of DFSP presents as an asymptomatic, skin-colored, slightly yellowish, violaceous, or pink macule or patch that, in time, becomes an indurated plaque. The size of the lesions ranges from 1 to 5 cm in diameter. The lesion enlarges slowly over months or years and may reach 20 cm or more in diameter. In time, protuberant nodules develop within the plaque (Fig. 32.1). The tumor frequently extends into the subcutaneous fat and may rarely invade the fascia, striated muscle, or bone. Cases of congenital

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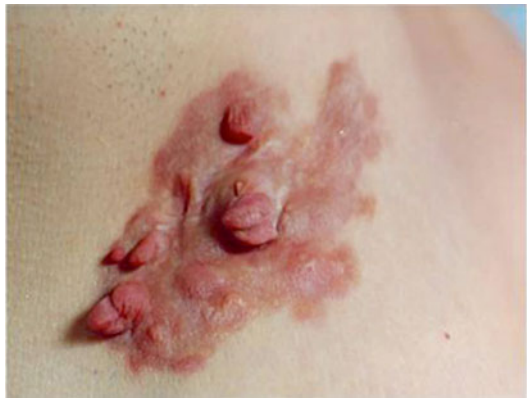

Fig. 32.1 Dermatofibrosarcoma protuberans. A typical presentation characterized by a slow-growing multinodular indurated plaque on the anterior trunk of a 30-year-old woman

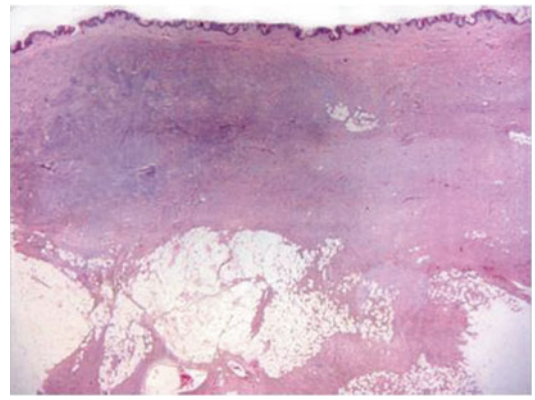

Fig. 32.2 The neoplasm occupies the entire dermis and extends into the septa and lobules of subcutaneous fat all the way down to the fascia

DFSP are exceedingly rare and usually present as atrophic or fibrous infiltrated plaques mostly localized on the trunk or proximal extremities. Due to its benign appearance, the correct diagnosis is often delayed until childhood or adulthood when nodular proliferation develops. DFSP may be confused clinically with many benign or malignant lesions, especially in the non-protuberant phase.

Pathology

DFSP is characterized by a dense proliferation of uniform spindle cells arranged into a distinctive, monotonous storiform pattern that occupies the entire dermis and extends into the septa and lobules of subcutaneous fat in a characteristic "honeycomb" pattern (Figs. 32.2, 32.3, and 32.4). The spindled cells that have monomorphous elongated nuclei and scanty pale cytoplasm are characteristically arranged in a "cartwheel" pattern (Fig. 32.5). Mitotic activity is scanty and does not exceed five mitoses per 10 high-power fields. Foci of myxoid degeneration may be present and the neoplasm exhibits only minimal, if any, necrosis. Apart from the conventional variant, DFSP can present with various histological patterns. Histological variants of DFSP include: giant cell fibroblastoma and pigmented, myxoid, myoid, atrophic, sclerotic, granular cell, and fibrosarcomatous DFSP. Giant cell fibroblastoma, a variant of DFSP described only in chil-

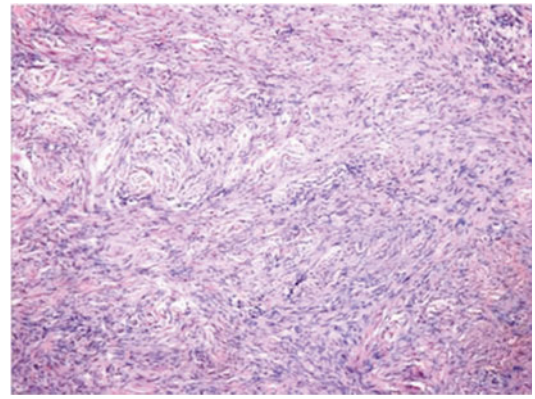

Fig. 32.3 DFSP is characterized by a dense proliferation of uniform spindle cells arranged into a distinctive, monotonous storiform or "cartwheel" pattern

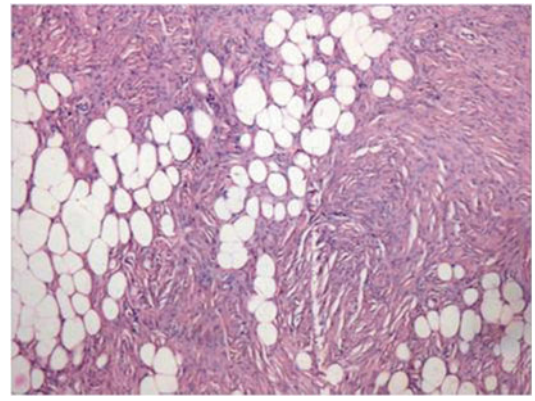

Fig. 32.4 The spindle cell proliferation extends into the septa and lobules of subcutaneous fat in a characteristic "honeycomb" pattern

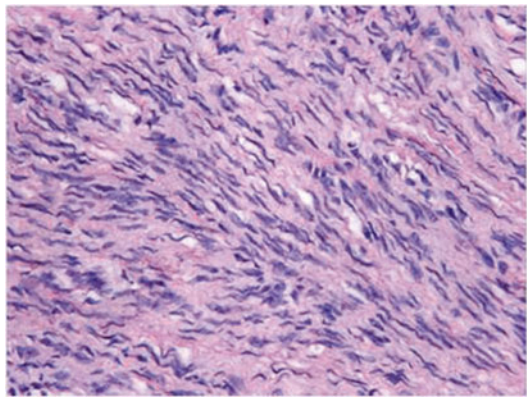

Fig. 32.5 The spindled cells have monomorphous elongated nuclei and scanty pale cytoplasm

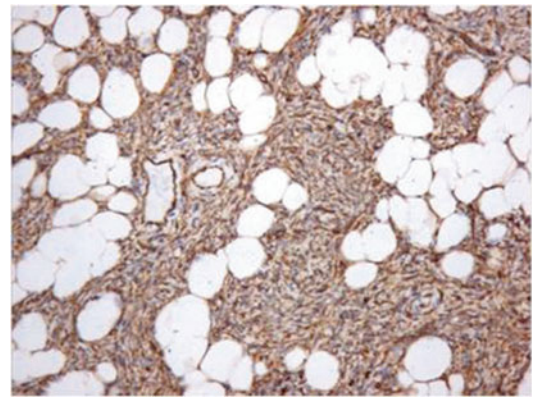

Fig. 32.6 The neoplasm is characterized by a positive reaction for CD34

dren, is composed of spindle cells usually arranged in a storiform pattern but frequently with areas of myxoid stroma and distinctive pseudovascular spaces lined by multinucleated giant cells. Pigmented DFSP, or Bednar tumor, has melanin-containing dendritic cells in variable concentrations among the spindle cells arranged in the typical storiform pattern. Myxoid DFSP exhibits prominent myxoid stromal changes that can efface the characteristic storiform pattern, a multinodular growth pattern, and a prominent capillary vasculature. Atrophic DFSP is less cellular than classic DFSP and is characterized by a marked atrophy of the middle dermis. Fibrosarcomatous DFSP exhibits areas of classic low-grade DFSP interspersed with more cellular areas where the cells are arranged in fascicles disposed in a herringbone pattern. These areas manifest significant cellular atypia and increased mitotic activity. Very rare cases of fibrosarcomatous DFSP with giant rosettes and DFSP with unusual sarcomatous transformation, which mimic undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma, have been reported. Exceptional cases of purely subcutaneous DFSP, histologically indistinguishable from typical DFSP, have been described. Areas resembling neurofibroma or schwannoma with nuclear palisading and even Verocay body formation can sometimes be encountered.

Immunohistochemistry: DFSP is characterized by a positive reaction for CD34 (Fig. 32.6), nestin, and vimentin and a negative reaction for factor XIIIa, D2-40, desmin, smooth muscle actin, CD117, and S-100.

Molecular Studies

COL1A1–PDGFB translocation can be detected by either FISH or RT-PCR techniques in most cases. Molecular studies are particularly useful for the diagnosis of unusual histopathologic subtypes and CD34-negative fibrosarcomatous DFSP. Also, the assessment of t(17;22) status is required prior to imatinib treatment.

Differential Diagnosis

The main differential diagnosis includes dermatofibroma, especially its cellular variant, neurofibroma, fibrosarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, and myxoid liposarcoma. Other entities to be considered are dermatomyofibroma, perineurioma, and plaque-like CD34-positive dermal fibroma (medallion-like dermal dendrocyte hamartoma). Dermatofibroma shows short fascicles of plump spindle cells and histiocytic cells

arranged in a haphazard array, inflammatory cells and siderophages, epidermal hyperplasia and basal hyperpigmentation of the overlying epidermis, and collagen entrapment at the periphery of the tumor. Involvement of the subcutaneous fat is usually limited, either in a vertical or radial fashion along the septa or with a smooth well-demarcated deep margin. CD34 and Factor XIIIa markers usually help in differentiation between the two tumors in most cases. The superficial part of DFSP may resemble neurofibroma and this may lead to some diagnostic difficulties, especially in superficial samples. However, neurofibroma lacks the storiform growth pattern and is positive for both CD34 and S100. Fibrosarcomas are usually deep-seated tumors, exhibit more cytologic atypia than DFSP, and are characterized by a herringbone arrangement of the cells. Compared to DFSP, malignant fibrous histiocytoma has more pleomorphic cells with prominent nuclei and atypical mitotic figures. Unlike DFSP, malignant peripheral nerve sheath tumor is composed of dense interlacing fascicles of atypical spindle cells alternating with hypocellular areas and shows characteristic perivascular whorling by tumoral cells. Plaque-like CD34-positive dermal fibroma (medallion-like dermal dendrocyte hamartoma)(DH) is a unique CD34+ and Factor XIIIa + spindle cell proliferation that can be confused with atrophic DFSP. It occurs predominantly but not exclusively in children as a slightly indurated or atrophic erythematous to brown plaque on the neck, trunk, and extremities. The lesion is usually confined to the reticular dermis, although it can occasionally extend into the subcutis. Unlike DFSP, the spindle cells in DH are arranged in concentric layers around vessels and peripheral nerves and are associated with fragmented or diminished elastic fibers and an increased number of mast cells. No evidence of COL1A1-PDGFB gene rearrangement is evident in DH.

Prognosis

The prognosis of DFSP is generally good. The tumor is locally aggressive but rarely metastasizes. Lymph node involvement is rare. The lung is the most common site of metastatic disease.

Treatment

Complete surgical excision is the mainstay of treatment in the form of either wide local excision (≥2 cm) or Mohs micrographic surgery. The adjuvant radiotherapy can avoid mutilation and functional deficit and can decrease the local recurrence rate when wide local excision is not possible. Chemotherapy is not efficient in controlling either metastatic or even locally recurrent DFSP. Imatinib mesylate, a tyrosine kinase inhibitor, may be of benefit for patients with locally advanced or metastatic DFSP, when other therapeutic options are limited.

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33 Atypical Fibroxanthoma/ Undifferentiated Pleomorphic Sarcoma (Superficial Malignant Fibrous Histiocytoma)

Franco Rongioletti

Introduction

Atypical fibroxanthoma (AFX) and malignant fibrous histiocytoma (MFH) are soft tissue fibrohistiocytic sarcomas with variable aggressiveness. There is considerable debate about the relationship between AFX and MFH, as histological and immunochemical differentiation is difficult. Some authors consider AFX as the superficial/dermal variant of MFH, now reclassified as "undifferentiated pleomorphic sarcoma (UPS)." Their different biological behavior is explained by the absence of ras-oncogene mutations in AFX, whereas MFH has both H- and K-ras gene mutations which contribute towards the less favorable prognosis of MFH. Otherwise, they have been classified as similar entities within a spectrum of fibrohistiocytic malignancies. This spectrum includes the dermal-based AFX; superficial MFH centered in the subcutis but which may extend into the dermis, fascia, and muscle; and deep MFH that originates in deep soft tissues and skeletal muscles but may involve adjacent superficial tissues. From a practical point of view, neoplasms that are confined to the dermis are diagnosed as AFX, whereas those which extended deeply beyond the dermis are diagnosed as UPS/ MFH.

AFX was first described by Helwig in 1963 as an atypical dermal spindle cell tumor with a good prognosis. It is characterized by its association with ultraviolet radiation, not only from a clinical aspect but also from a molecular aspect based upon the fact that there is a p53 gene mutation at pyrimidine sites and immunoexpression of pyrimidine dimers. Increased telomerase expression allowing cells to proliferate continuously without entering apoptosis or senescence has been found both in AFX and UPS.

MFH was first described in 1963 and then classified by O'Brien and Stout in 1964 as a distinct histological type of soft tissue sarcoma. Actually, tumors with similar pathological features to AFX but deep subcutaneous invasion, necrosis, and/or lymphovascular or perineural invasion are better regarded as UPS/MFH of the skin and are associated with a worse prognosis. The etiopathogenesis of UPS/MFH is unknown, but the relationship with sun exposure is controversial.

Clinical Features

AFX typically presents as a skin-colored or brown red and frequently eroded nodule on severely sun-damaged skin in the head and neck of patients in the seventh/eighth decade of life. AFX has a predominance in males (70 %), is usually less than

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Table 33.1 Comparison of the clinical, histological, and immunohistochemical features of atypical fibroxanthoma and malignant fibrous histiocytoma

	Atypical fibroxanthoma	Malignant fibrous histiocytoma
Clinical		
Age of onset (years)	>70 (75 %) 20–40 (25 %)	50–70
Risk factors	UV radiation X-ray radiation Immunosuppression Trauma	X-ray radiation ?UV radiation
Site	Head and neck (75 %), trunk and limbs (25 %)	Lower and upper extremities (70–75 %) Head and neck (10 %)
Gross appearance	Solitary nodule <2 cm ± ulceration	Multilobulated nodule 5–10 cm ± ulceration
Local recurrence	7–12 %	19–31 %
Metastases	Rare	10–55 % Lungs (90 %), lymph nodes (12 %), bone (8 %), liver (1 %)
Histological		
Architecture	Dermal nodule	Proliferation centered in the subcutaneous tissue (10 %)
	Extension to superficial subcutis (uncommon)	Extension to deep subcutaneous tissue, fascia, and muscle
	Fascicular pattern	Storiform pattern
	Necrosis (rare)	Necrosis (common)
Cell type	Spindle or round cells	Spindle cells Foam cells and giant cells
	Pleomorphism	Marked pleomorphism
	Atypical mitotic figures	Atypical mitotic figures Myxoid foci
Immunohistochemical		
S100, HMB45, CD34, cytokeratin, and Factor XIIIA	Negative	Negative
Muscle-specific actin, CD68, vimentin, α1-antichymotrypsin and α1-antitrypsin, CD10	Positive	Positive
CD74	Weak positive	Strong positive
CD99	Variable positivity from 10 % to 94 %	Variable positivity (15 %)

2 cm in size, and is associated with ulceration and bleeding as it enlarges (Fig. 33.1). A less common form lacking association with sun exposure occurs on the limbs and trunk in younger patients in the fourth decade of life. AFX may develop in immunocompromised patients such as in organ transplant recipients or in young patients with xeroderma pigmentosum. There are reported cases of metastatic AFX; however, these are likely to be cases of UPS or other mesenchymal malignancies.

UPS/MFH occurs most commonly in males during the sixth and seventh decades of life. The most common locations are the extremities followed by the head and neck region and trunk. It presents as a painless enlarging nodule, which may be 5–10 cm in size, with or without ulceration. Up to 25 % of cases may arise in subcutaneous tissues, although less than 10 % are confined to the subcutis without underlying fascial involvement.

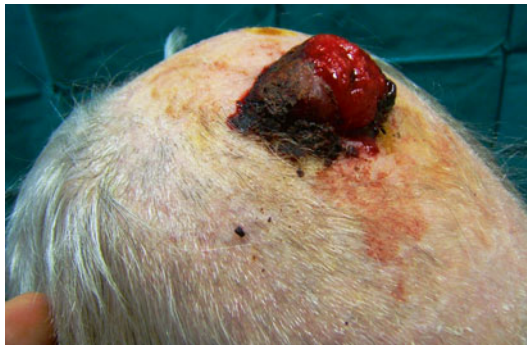

Fig. 33.1 Atypical fibroxanthoma. A *brown red*, eroded nodule on severely sun-damaged skin in the scalp of an old patient

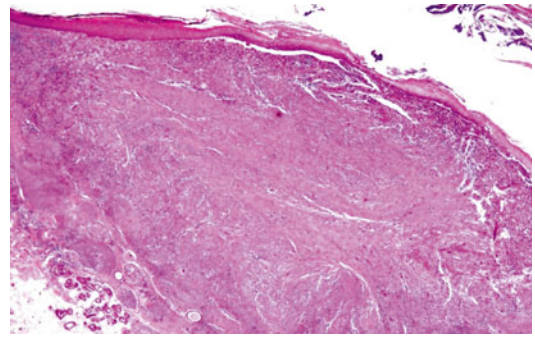

Fig. 33.2 Atypical fibroxanthoma. A cellular dermal tumor reaching the subcutaneous layer under an ulcerated epidermis

Pathology

AFX is a cellular dermal tumor with circumscribed borders (Fig. 33.2). The tumor may spare the epidermis (grenz zone), while up to 50 % of the lesions are ulcerated (Figs. 33.2 and 33.3). AFX is comprised of spindle, plump, epithelioid, and bizarre cells, in varying proportions, arranged in haphazard, fascicular, or storiform patterns (Figs. 33.3 and 33.4) . Spindle cells predominate in 72 percent of AFX cases. Foam cells as well as multinucleated giant and monster tumor cells may be observed (Fig. 33.5). Atypical mitoses are found and also, less commonly, tumor necrosis. The presence of blood-filled spaces and intratumoral hemorrhage gives sometimes the tumor a pseudoangiomatous appearance. Solar elastosis, stromal fibrosis, a dense lymphocytic infiltrate, and areas of regression are the common features. Numerous histological variants have been reported, including a clear cell, desmoplastic or keloidal, granular, angiomatoid, hemosiderotic (pigmented), and myxoid, among others.

Histologically, UPS/MFH is characterized by spindle-shaped or round cells with multinucleation, pleomorphism, and numerous mitoses and shows a storiform pattern indistinguishable from that of AFX. Prominent myxoid stromal change may resemble myxofibrosarcoma. If a tumor is larger than 2 cm, extensively involves the subcutis, penetrates the fascia and muscle, or displays necrosis or

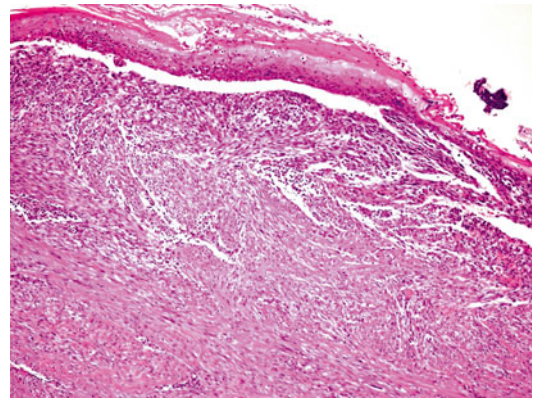

Fig. 33.3 Atypical fibroxanthoma. The tumor is comprised of predominant spindle, plump cells arranged in haphazard, fascicular, or storiform patterns

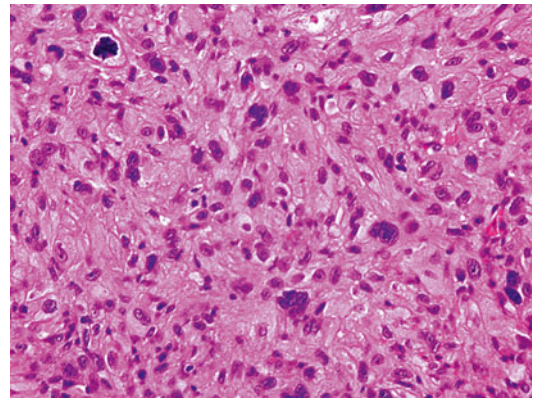

Fig. 33.4 Atypical fibroxanthoma. Bizarre cells in varying proportions with atypical mitoses

lymphovascular invasion, it should be diagnosed as UPS/MFH (Figs. 33.6, 33.7, and 33.8).

AFX and UPS/MFH also share similar immunochemical features. Both cells in AFX and MFH are negative for melanoma markers, hematopoietic markers (e.g., CD34), and epithelial markers (e.g., cytokeratins) but are positive for smooth muscle actin, vimentin, CD68, and CD10, the notable difference being strong positivity for CD74 shown by UPS/MFH. The positivity for CD99 is variable. There are also similarities in the expression of the proliferation markers of PCNA and MIB-1. The findings that LN-2 (CD74) immunopositivity is a specific marker for UPS/MFH or indicative of prognosis for AFX have not been confirmed. Comparative genomic hybridization (CGH) analysis also demonstrated similarities between AFX and UPS/MFH with genetic alterations on chromosomes 9p and 13q.

The comparison between the clinical, histological, and immunohistochemical features of AFX and UPS/MFH is outlined in Table 36.1.

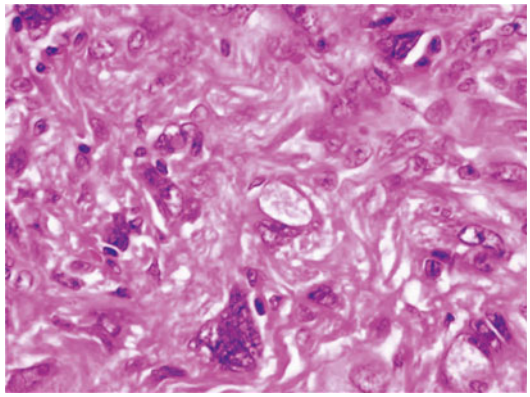

Fig. 33.5 Atypical fibroxanthoma foam cells as well as multinucleated giant and monster tumor cells may be observed

Differential Diagnosis

The diagnosis of AFX and UPS/MFH is by exclusion, as there are no specific markers. AFX and MFH are considered in the differential diagnosis with spindle cell squamous cell carcinoma (SCC), spindle cell malignant melanoma, leiomyosarcoma, and dermatofibrosarcoma protuberans. The latter is characteristically CD34 positive. Fibrosarcoma is generally less pleomorphic and shows a herring-bone pattern. Malignant peripheral nerve sheath tumor is often associated with nerves and may show S-100 protein positivity. Leiomyosarcoma is defined as a sarcoma showing more than two of four known markers of smooth muscle differentiation. Aberrant expression of endothelial markers such as CD31 and FLI1 in AFX may lead to an erroneous diagnosis of angiosarcoma.

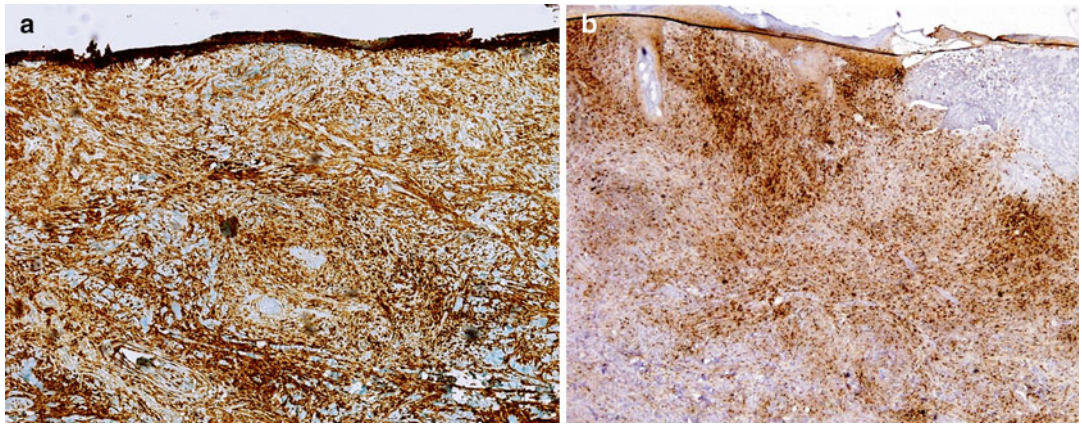

Fig. 33.6 Atypical fibroxanthoma. (**a**) The proliferating cells are positive for CD10. (**b**) Positivity for CD68

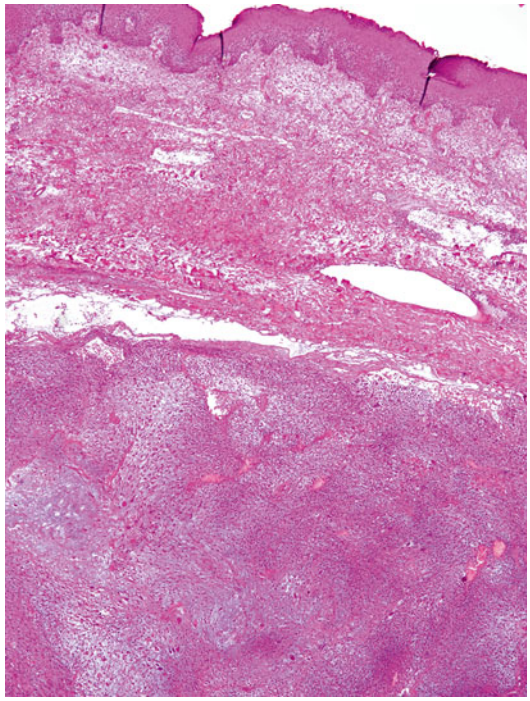

Fig. 33.7 Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma. A large, nodular tumor extending into the dermis and deep subcutaneous adipose tissue

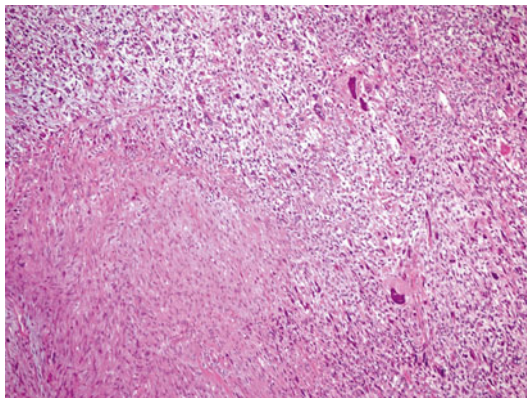

Fig. 33.8 Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma. The tumor is composed of storiform, myxoid, and pleomorphic areas

Prognosis

AFX is considered a tumor of intermediate malignant potential. The recurrence rate has been reported to range between 5 % and 10 %. Metastases are uncommon and occur in approximately 1 % of reported cases. UPS/MFH is much more aggressive than the AFX, and some argue that cases of "metastatic AFX" are actually MFH. The rate of local recurrence for MFH ranges between 19 % and 31 %, and metastasis occurs in 31–35 % of patients after the tumor resection. The 5-year survival rate ranges from 65 to 70 %. The common sites of metastasis are the lung (90 %), bone (8 %), and liver (1 %). The prognosis depends to a great extent upon the tumor depth. Hence, deep MFH is the most aggressive of the fibrohistiocytic tumors, with a high local recurrence rate and a significant metastatic risk, while AFX exhibits a relatively benign clinical course.

Treatment

The recommended treatment for AFX is complete surgical excision with 1 cm margins and excision into the subcutaneous tissue to ensure a tumor-free margin. Nonsurgical candidates may benefit from radiotherapy. Wide surgical excision with at least 2 cm margins is the standard treatment for UPS/MFH with consideration to sentinel lymph node and dissection of regional nodes. Inadequate surgical margins may lead to local recurrence. Despite a 3–5 cm excision margin, local recurrence and/or metastasis may occur in 40–50 % cases, mostly within 2 years. Because of the high incidence of local recurrence and/or metastasis, adjuvant radiotherapy is recommended. The efficacy of chemotherapy remains questionable. Mohs micrographic surgery has been suggested to reduce the rates of recurrences.

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Epithelioid Sarcoma

34

Irina Margaritescu, A. Doru Chirita, and Florina Vasilescu

Introduction

Epithelioid sarcoma (ES) is a rare soft tissue sarcoma, first characterized as a distinct clinicopathologic entity by Enzinger in 1970, which presents in the two main clinicopathologic settings. The classic or distal type occurs mostly on the extremities of young adults as a slowly growing tumor within the dermis or subcutis. The proximal type occurs predominantly in older patients as deeply infiltrative masses in axial locations. However, features of classic and proximal types can overlap and each may occur in either proximal or distal locations (Fig. 34.1). Proximal-type ES is associated with a more aggressive clinical course than the classic type.

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Clinical Features

ES presents as a slowly growing dermal nodule that may rapidly ulcerate, a lobular subcutaneous tumor, or as a poorly defined deeply located mass. It may be asymptomatic or may cause paresthesia, pain, or muscular wasting. The classic type presents mainly in adolescents and young adults, while the proximal type affects mostly middle-aged or older adults. However, the neoplasm may occur at any age (range 11–93 years). Occurrence in children is uncommon. Males are more affected than females. The tumor measures less than 5 cm in diameter (range 1–30 cm). The time delay before diagnosis ranges from 2 to 96 months.

Classic-type ES typically occurs in the distal extremities, especially hand and forearm, but may also involve the leg, foot, and knee. It presents as a slowly growing, solitary or multiple, dermal or subcutaneous tumor, often accompanied by superficial ulceration, hemorrhage, and necrosis. The tumor has a tendency for extensive spread along blood vessels, nerves, and fascia, with appearance of satellite nodules in a sporotrichoid distribution. Proximal-type ES is less common and appears mainly in axial or proximal regions, including the limb girdles, pelvis, perineum, genitalia, mediastinum, and trunk. It presents as a deep, infiltrative mass that can extend along tendon sheaths or aponeuroses. ES may mimic other benign or malignant diseases, including perforating granuloma annulare, Dupuytren's disease, and melanoma.

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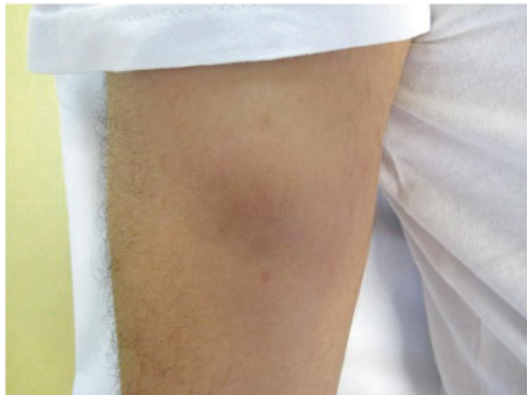

Fig. 34.1 Epithelioid sarcoma. A slow-growing indurated subcutaneous tumor on the left arm of a 33-year-old man for 5 years (Courtesy of Cristina Cotruta, M.D. and Konstantinos Koutsioukis, M.D.)

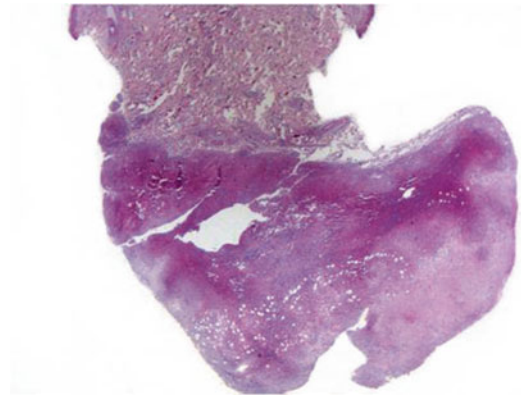

Fig. 34.2 The multinodular tumor with deeply eosinophilic appearance is located in the subcutaneous fat with minimal extension into the dermis

Pathology

Classic-type ES is usually situated in the dermis and/or subcutis and has a nodular or diffuse outline. A "geographic" appearance with multiple nodules of intensely eosinophilic polygonal, epithelioid, or spindle-shaped cells associated with central necrosis is apparent even at scanning magnification (Fig. 34.2). Necrosis in the center of nodules may be a prominent feature and may lead to confusion with a granulomatous process (Fig. 34.3). At the periphery of the nodules, the tumor cells tend to be more spindle shaped (Fig. 34.4). The cells show variable pleomorphism and only a few mitotic figures (Fig. 34.5). Local infiltration along tendons, fascial planes, and neurovascular bundles is often present. These changes are more pronounced in advanced stages or in recurrent tumors and may not be evident in early lesions. The superficial tumors show less pleomorphism and a lower mitotic activity than deeply seated tumors. Proximal-type ES is characterized by sheets of large epithelioid cells, with vesicular nuclei and prominent nucleoli (Fig. 34.6). Cells with abundant glassy cytoplasm, eccentric nuclei, and prominent nucleoli (rhabdoid morphology) are frequently encountered. Some cases show a vague fibrinoid or myxoid pattern of degeneration. In a few cases, an angiomatoid or angiosarcoma-like pattern is

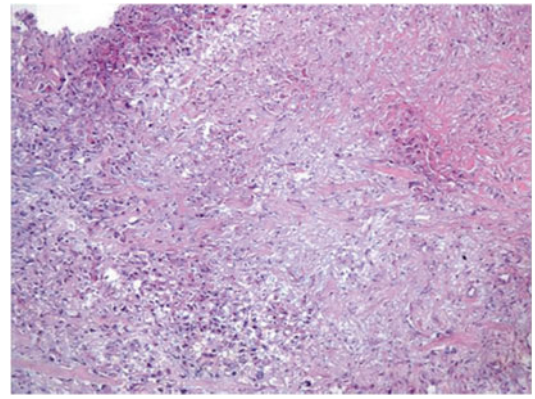

Fig. 34.3 There is extensive necrosis in the center of nodules which may lead to confusion with a granulomatous process

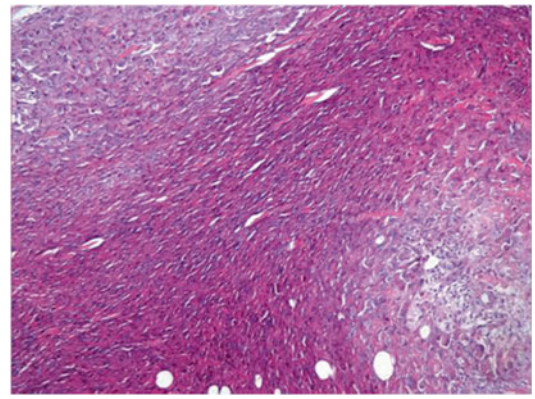

Fig. 34.4 The tumor is composed of both epithelioid and spindle cells

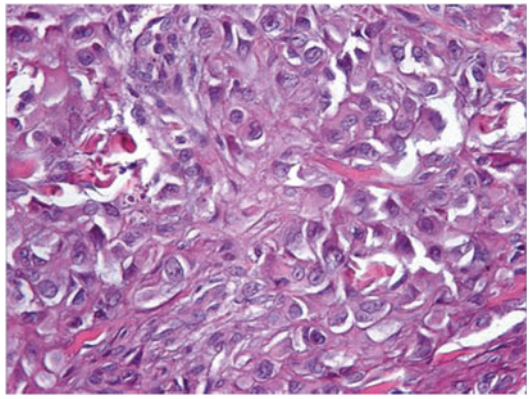

Fig. 34.5 Some areas display epithelioid cells with bland cytologic appearance

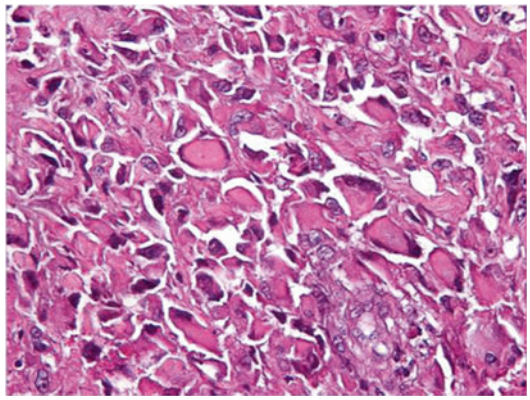

Fig. 34.6 Other areas show sheets of larger epithelioid cells with a rhabdoid morphology

seen. A "fibroma-like" variant has also been described. Focal calcification is an unusual feature.

Immunohistochemistry: ES characteristically exhibits immunohistochemical reactivity for both epithelial and mesenchymal markers. ES is characterized by a positive reaction for vimentin, cytokeratin, and EMA. CD34 is positive in almost half of all cases. The combination of vimentin, cytokeratin, EMA, and CD34 positivity is virtually diagnostic for ES (Fig. 34.7). A strong reactivity for CA-125 has been reported. CK20, CEA, S-100, HMB-45, SMA, LCA, and CD31 are negative. Proximal- and distal-type ES have a similar immunohistochemical profile. Loss of nuclear INI1 expression is seen in the majority of cases in both proximal- and distal-type ES.

Molecular studies: The most consistent cytogenetic abnormality is the loss of heterozygosity of chromosome 22q. Loss of INI1 (BAF47) nuclear expression encoded by *SMARCB1* (*INI1*) at 22q11.23 is characteristic.

Differential Diagnosis

In early stages of the disease, due to its bland appearance, epithelioid sarcoma may be mistaken for an inflammatory process, such as granuloma annulare, necrobiosis lipoidica, or rheumatoid nodules. However, the cells of epithelioid sarcoma are more sharply defined, more eosinophilic, and stain positive for cytokeratins, EMA, and CD34 and negative for CD68. Early stage epithelioid sarcoma can also be confused with a necrotizing infectious granuloma, nodular fasciitis, fibrous histiocytoma, and fibromatosis.

Epithelioid sarcoma may also be mistaken for a wide array of epithelioid-appearing malignant neoplasms. These include epithelioid malignant peripheral nerve sheath tumor, melanoma, clear cell sarcoma, epithelioid hemangioendothelioma/angiosarcoma, epithelioid sarcoma-like hemangioendothelioma, epithelioid leiomyosarcoma, synovial sarcoma, alveolar soft-part sarcoma, embryonal rhabdomyosarcoma, large-cell anaplastic lymphoma, metastatic carcinoma, mesothelioma, and extrarenal rhabdoid tumor. Appropriate immunohistochemistry using a large panel of antibodies coupled with molecular and ultrastructural studies and a careful clinicopathologic correlation allows for the correct diagnosis in each and every case.

Prognosis

ES has a high risk for local recurrence and metastasis. The most common sites of metastasis are the lung, regional lymph nodes, and scalp. Features

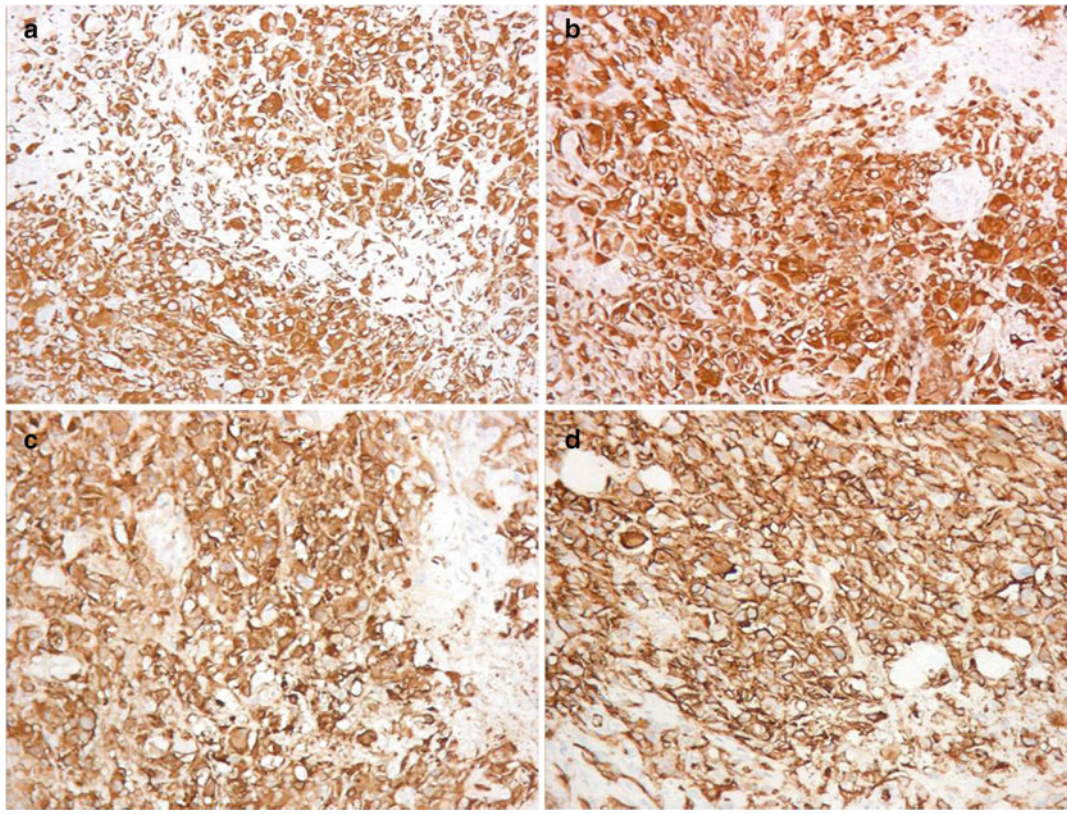

Fig. 34.7 The cells stain strongly with (**a**) vimentin, (**b**) cytokeratin, (**c**) EMA, and (**d**) CD34. This combination is virtually diagnostic for ES

associated with poorer prognosis include male gender, older age at diagnosis, proximal location, large tumor size (>5 cm), increase tumor depth, high mitotic index, vascular invasion, hemorrhage, necrosis, lymph node metastasis, and local recurrence due to inadequate initial excision. Overall 5-year survival rates for classic type of ES range from 50 % to up to 85 %.

Treatment

Early and complete resection of the neoplasm with clear surgical margins is the recommended treatment for epithelioid sarcoma. Amputation should also be considered if the tumor is situated in the fingers or toes, or in cases with multiple local recurrences. However, it is currently accepted that a limb-conserving surgery combined with adjuvant radiotherapy and multiagent chemotherapy may achieve effective local control of the disease, excellent functional outcome, and a survival equivalent to that of radical amputation. Sentinel node biopsy, followed by regional lymph node dissection when positive, may be of benefit. Other treatment options such as isolated limb chemotherapy with tumor necrosis factor and melphalan have shown excellent results.

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Part VI

Tumours of Vessels

Composite Hemangioendothelioma

35

Elisa Cinotti and Franco Rongioletti

Introduction

Composite hemangioendotheliomna (CHE) is a low-grade malignant vascular tumor of soft tissues showing varying combinations of benign, low-grade malignant, and malignant vascular components. Occasionally, it has been described in the mediastinum, spleen, and kidney. Fewer than 30 cases have been reported.

Clinical Features

The tumors typically manifests as an infiltrative mass or ill-defined swelling on a distal limb involving multiple parts at the same time, such as the forearm/hand. The size of individual tumors ranges from 0.7 to 30 cm. Patient age ranges from newborns to old adults with a mean age of 42 years.

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Pathology

The neoplasm is made of a complex admixture of histological components resembling various vascular lesions (Fig. 35.1). The predominant components, present in all cases, are similar to retiform HE and epithelioid HE. Angiosarcoma-like areas and lymphangioma-like areas are also found as well as areas of spindle cell hemangioma, cavernous hemangioma, or arteriovenous malformation. The 2 congenital cases, which exhibited multiple lesions, had angiosarcoma-like components and an angiomatosis-like growth pattern. One patient each was associated with Kasabach-Merritt or Maffucci syndrome. Immunohistochemically, all tumors showed expression of at least two endothelial markers (CD31, CD34, and/or factor VIII-related antigen). Immunoreactivity for Prox-1 in one case supports a lymphatic line of differentiation.

Differential Diagnosis

Cutaneous angiosarcoma usually occurs in the head and neck area of elderly patients and presents as an ill-defined and infiltrative ecchymotic patch or plaque. It may also develop in areas of chronic lymphedema or previous radiation therapy.

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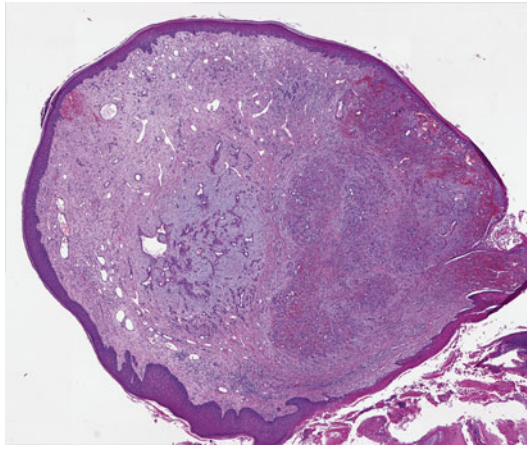

Fig. 35.1 Composite hemangioendothelioma. The neoplasm is made of a complex admixture of histological components resembling various vascular lesions such as epithelioid hemangioendothelioma, spindle cell hemangioma, as well as angiosarcoma-like areas and lymphangioma-like areas (Courtesy of Heinz Kutzner, MD, Friedrichshafen)

Prognosis

CHE has a tendency for local recurrence but low metastatic potential. There was no difference of biological behavior among cases with various combinations of histology. The presence of "angiosarcoma-like foci" and a prior history of long-standing lymphedema suggest that CHE may in fact be a low-grade angiosarcoma that behaves prognostically better than conventional angiosarcoma.

Treatment

Total excision when feasible is considered the first-line treatment. Postoperative radiotherapy, preoperative or postoperative chemotherapy, and therapy with interferon alfa-2b have been used with variable results.

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Epithelioid Hemangioendothelioma

36

Elisa Cinotti and Franco Rongioletti

Introduction

Epithelioid hemangioendothelioma (EHE) is an intermediate-grade vascular tumor of endothelial origin first reported by Weiss and Enzinger in 1982. It is most commonly found in superficial or deep soft tissues but can arise in any organ such as the lungs and liver. Skin involvement is rare and only 10 % arise within the dermis. About 19 cases of EHE with skin involvement have been reported in the literature.

Clinical Features

The neoplasm affects equally both sexes during the second and third decades of life and rarely children. It presents as a single, rarely multiple, erythematous papule, nodule, plaque, or nonhealing ulcers sometimes associated with pain (Fig. 36.1). Most of the cases show multifocal localization. The lower extremities are the preferential site. Rare challenging presentations mimicking a verruca vulgaris have been reported. Possible associations with trauma, therapeutic radiation, and hormonal factors have been suggested.

Pathology

The tumor is made by cords, strands, and solid aggregates of epithelioid, round to slightly spindle-shaped endothelial cells with abundant pale eosinophilic cytoplasm and round vesicular nucleus with minimal pleomorphism embedded in a fibromyxoid or sclerohyaline stroma (Fig. 36.2). Intracytoplasmic vacuolization with occasional intraluminal erythrocytes reminiscent of primitive vessels is a diagnostic clue (Figs. 36.3 and 36.4). The so-called high-risk EHE demonstrates classic histopathologic features and a size larger than 3 cm or >3 mitotic figures per 50 high-power fields. Cases are always positive for at least one vascular endothelial marker (factor VIII-related antigen, CD31, CD34), but not usually all. Podoplanin and FLI-1 may also be positive. The cytokeratin is expressed in one fourth of patients and CD10 and actin positivity may be found. Electron microscopy reveals the endothelial nature of the tumor cells surrounded by basal lamina, dotted with surface pinocytotic vesicles

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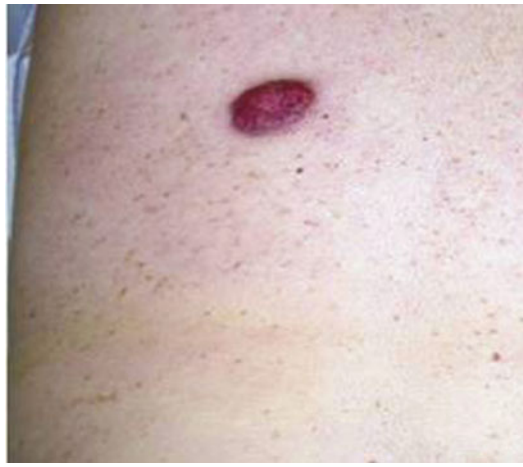

Fig. 36.1 Epithelioid hemangioendothelioma. A single, erythematous, painful nodular plaque on the trunk. Although a vascular lesion can be considered, the diagnosis is a histological one

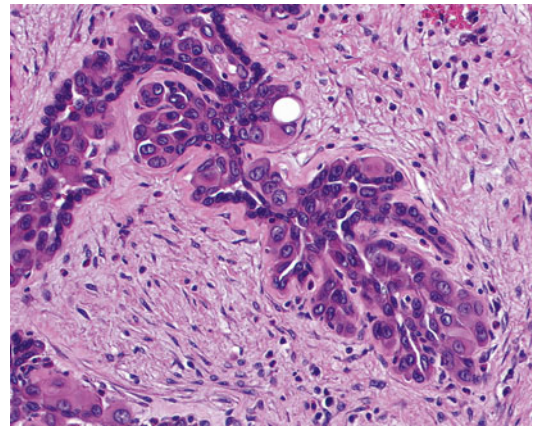

Fig. 36.3 Epithelioid hemangioendothelioma. The tumor is made by epithelioid, round to slightly spindle-shaped endothelial cells with abundant pale eosinophilic cytoplasm and round vesicular nuclei with minimal pleomorphism and formation of vacuoles (Courtesy of H.Kutzner, *Friedrichshafen*)

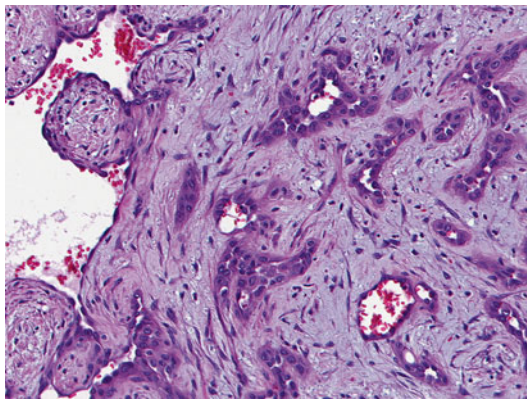

Fig. 36.2 Epithelioid hemangioendothelioma. Proliferating cells extend centrifugally from the vessel, infiltrating the surrounding stroma as cords, strands, and solid aggregates. Note vascular space differentiation (Courtesy of H.Kutzner, *Friedrichshafen*)

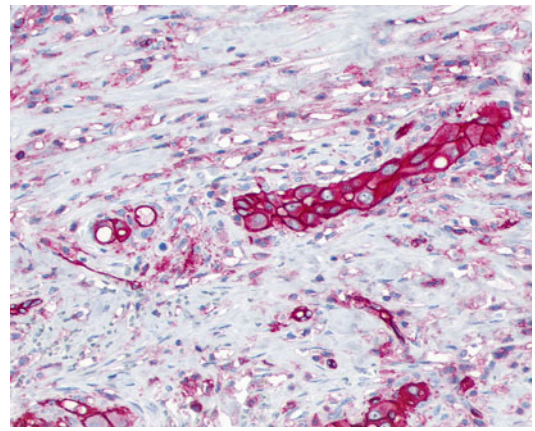

Fig. 36.4 Epithelioid hemangioendothelioma. The tumor cells are strongly positive for the endothelial cell marker FLI-1. Many cells contain intracytoplasmic vacuoles that displace the nucleus and resemble signet-ring cells (Courtesy of H.Kutzner, *Friedrichshafen*)

and intracytoplasmic lumina, and occasionally containing Weibel-Palade bodies. The chromosomal translocation involving chromosomes 1 and 3 (t[1;3][p36.3;q25]) and resulting in the *WWTR1-CAMTA1* fusion gene is known to occur in EHE.

Differential Diagnosis

Clinically, EHE has to be differentiated from a hemangioma, pyogenic granuloma, and arteriovenous malformation. From its histological

features, it must be differentiated from epithelioid hemangioma and epithelioid hemangiosarcoma. The former shows well-formed blood vessel and inflammatory features, while the latter exhibits anastomosing irregular vascular channels with endothelial cell atypia and multilayering.

Prognosis

The prognosis of EHE is variable and uncertain. Cutaneous EHE have a more favorable outcome than the deeper form, and some authors have suggested that EHE of the soft tissue should be better regarded as a fully malignant, rather than borderline, vascular neoplasm. Isolated EHE of the skin probably behaves in a more benign fashion. EHE displaying features of cellular atypia, mitotic activity (>1 mitotic figure per 10 high-power fields), necrosis, and extensive spindling is related to an aggressive course and poor prognosis with an increased rate of metastasis (25 % of cases) and a poor 5-year survival (59 %).

Treatment

Complete surgical excision is recommended with evaluation of regional lymph nodes. A diagnosis of EHE should lead to a full assessment of the extension of the disease to detect any internal involvement. Adjuvant treatment with interferon therapy and radiotherapy or chemotherapy may be used for incompletely removed tumors or in case of multisystem involvement.

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Kaposiform Hemangioendothelioma

37

Elisa Cinotti and Franco Rongioletti

Introduction

Kaposiform hemangioendothelioma (KHE), first described by Zuckerberg et al. in 1992, is a rare, locally aggressive vascular neoplasm that mainly occurs in children and presents common histopathologic features to both hemangiomas and Kaposi sarcoma. The incidence is estimated at 0.07/100,000 children per year. It generally originates on the skin and soft tissue, usually affecting deeper tissue by infiltrative growth. Although visceral involvement is uncommon, the occurrence of KHE within the bone and retroperitoneal or mediastinal spaces has been described. About 160 cases have been reported in the literature. In more than 70 % of cases, KHE is associated to Kasabach-Merritt syndrome (KMS) and lymphangiomatosis. KMS designs patients in which the neoplasm occur in association with profound thrombocytopenia (<20,000), consumptive coagulopathy, and hypofibrinogenemia with fibrin degradation products resulting from the localized intravascular coagulation in the tumor.

Clinical Features

KHE presents during early childhood (most often in the first years of life) with fewer than 20 adult patients reported in the literature, and it is more common in males. It appears as one or multiple violaceous subcutaneous masses with ill-defined borders and a purpuric, bruised appearance. In most cases, the tumor involves the extremities and trunk (75 % of cases). Approximately 10 % of KHE do not involve the skin. The retroperitoneum is the most frequent extracutaneous location, followed by the muscle, bone, and thoracic cavity. Over time, especially in cases associated with KMS, the tumor becomes indurated and firm with a red purple hue, ecchymoses, and petechiae.

Pathology

The features of KHE resemble both a capillary hemangioma and Kaposi sarcoma (Figs. 37.1, 37.2, and 37.3). KHE shows infiltrating sheets composed of variably spindled endothelial cells, slit-like vascular channels reminiscent of Kaposi sarcoma, microthrombi, hemosiderin deposition,

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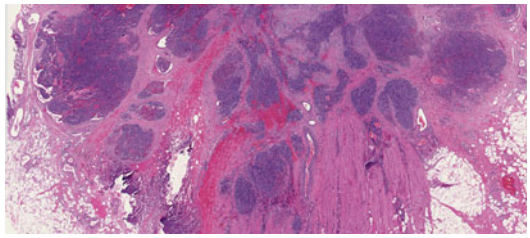

Fig. 37.1 Kaposiform hemangioendothelioma. Irregular tumor nodules growing in an infiltrative fashion and evoking a dense hyaline stromal response (Courtesy of H. Kutzner, *Friedrichshafen*)

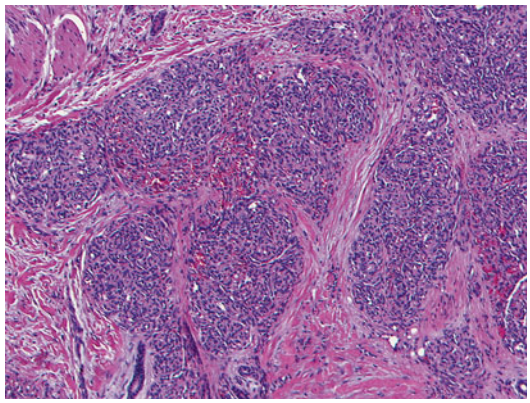

Fig. 37.2 Kaposiform hemangioendothelioma. Tumor nodules composed with well-canalized areas alternating with poorly canalized and solid-appearing areas resembling a capillary hemangioma (Courtesy of H.Kutzner, *Friedrichshafen*)

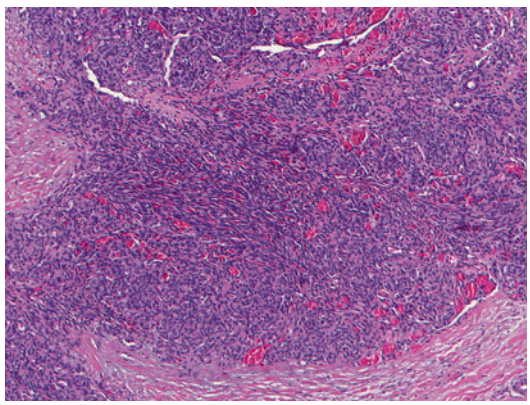

Fig. 37.3 Kaposiform hemangioendothelioma. Infiltrating sheets composed of variably spindled endothelial cells and slit-like vascular channels reminiscent of Kaposi sarcoma (Courtesy of H.Kutzner, *Friedrichshafen*)

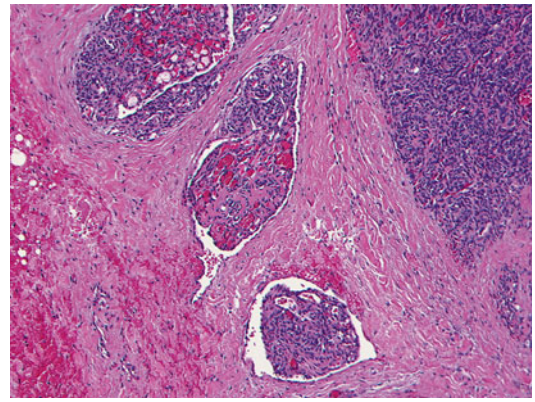

Fig. 37.4 Kaposiform hemangioendothelioma. Some areas show a glomeruloid pattern (Courtesy of H.Kutzner, *Friedrichshafen*)

edema, fibrosis with scanty inflammatory cells, and abnormal lymphatic channels. Tumor nodules surround areas that are well canalized alternating with solid-appearing areas mimicking a capillary hemangioma. Some areas may show a glomeruloid pattern reminiscent of renal glomeruli (Fig. 37.4). The rate of mitosis is variable but usually is not high. Endothelial cells in nodules are CD31, CD34, D2-40, PROX-1, and FLI1 positive but negative for GLUT1 and LeY (juvenile hemangioma-associated antigens). Focal actin positivity may be seen. HHV-8 transcripts are not identified.

Differential Diagnosis

The diagnosis is based upon the histology and on its correlation with clinical features, in particular the depth of the lesion. The relationship between KHE and tufted angioma is controversial. The "cannon ball" distribution of skin nodules and their "tufting" into ectatic spaces are characteristic of tufted angioma. In KHE, the tumor nodules coalesce, enlarge, and assume a widely infiltrative pattern within the fibroblastic stroma, a feature not observed in tufted angioma. A different pattern of expression of D2-40 has been reported as useful to distinguish the two entities. Nevertheless, the morphological overlap between KHE and tufted angioma has led to consider the

two lesions into the same disease spectrum and that tufted angioma may represent a minor form of KHE.

Prognosis

KHE tend to be locally invasive, but are not known to produce distant metastases. Several factors are associated with the outcome of patients with KHE: accessibility to surgical excision; location (cutaneous versus deep involvement); size of tumoral mass; clinical response to interferon, glucocorticoids, or propranolol; and the presence of lymphangiomatosis and KMS. The latter phenomenon is directly responsible for the significant morbidity and mortality, including hemodynamic instability, local invasion, and compression of vital structures.

Treatment

Surgical excision is the treatment of choice for tumors of limited size. However, since the margins are often poorly defined, surgical excision is often incomplete. For tumors that are not resectable, prednisone, vincristine, sirolimus, interferon alpha, propanol, and antiplatelet drugs have been used. However, no single regimen leads to the complete resolution of the tumor. The management of infants with KHE associated with Kasabach-Merritt phenomenon involves primarily the treatment of the tumor responsible for the coagulopathy and supportive measures to maintain hemostasis.

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Retiform Hemangioendothelioma

38

Elisa Cinotti and Franco Rongioletti

Introduction

Retiform hemangioendothelioma (RH) is a distinctive variant of intermediate (rarely metastasizing) vascular tumor of the soft tissue. Since its original description in 1994 by Calonje et al., only about 35 cases have been reported.

Clinical Features

It presents as a red/bluish slowly growing plaque or nodule usually less of 3 cm in size. Multiple lesions have been described on anecdotal basis. It involves predominantly the skin and subcutaneous tissue and is most commonly found in the distal extremities, particularly the lower limb. Isolated cases have been reported on the head, trunk, and penis. Although most cases of RH are idiopathic, it is rarely associated with radiation therapy and chronic lymphedema. In a single case, multiple lesions developed in different anatomic sites. The age range is wide, but it usually affects young adults or children; males and females are equally affected.

Pathology

Histopathologically, it consists of elongated arborizing blood vessels involving the dermis and arranged in a pattern reminiscent of the normal rete testis architecture (Fig. 38.1). Hence, the lesion was named retiform hemangioendothelioma. These arborizing blood vessels are lined by monomorphic endothelial cells with prominent protuberant nuclei having a characteristic hobnail-like or tombstone-like appearance (Figs. 38.2 and 38.3). Prominent lymphocytic infiltrate often obscures the vascular proliferation. In addition to a retiform pattern, solid tumor areas composed of epithelioid or spindle cells and dilated vascular channels with intraluminal papillary projections similar to those seen in Dabska's tumor may also be found. The term hobnail hemangioendothelioma has been proposed for vascular neoplasm with overlapping features of both Dabska's tumor and retiform hemangioendothelioma (Fig. 38.4). Cytologic atypia is minimal, and mitotic figures are rare. Vacuolated cells are rarely present. RH can be a part of a composite hemangioendothelioma.

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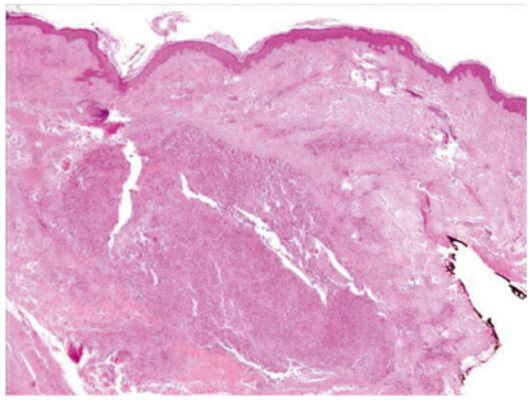

Fig. 38.1 Retiform hemangioendothelioma. A vascular tumor composed of elongated arborizing blood vessels involving the dermis and subcutis

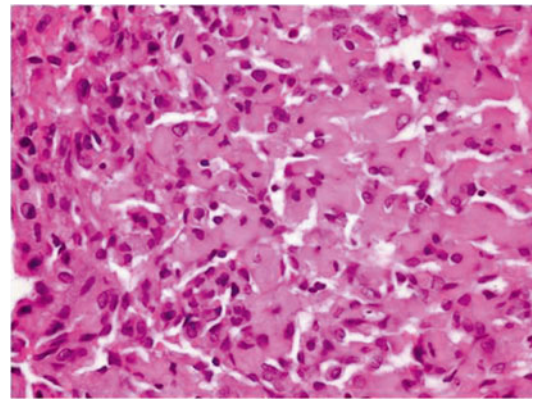

Fig. 38.3 Retiform hemangioendothelioma. The arborizing blood vessels are lined by monomorphic endothelial cells with prominent protuberant nuclei having a characteristic hobnail-like appearance

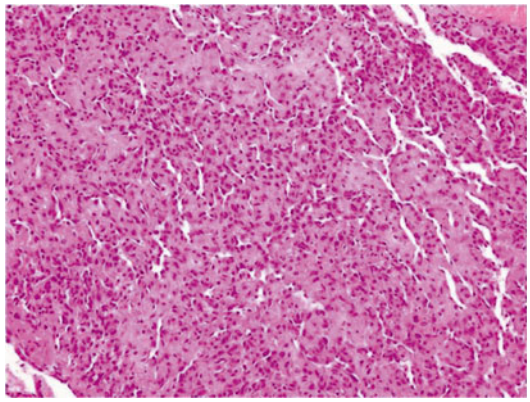

Fig. 38.2 Retiform hemangioendothelioma. The arborizing blood vessels are arranged in a pattern reminiscent of the normal rete testis architecture

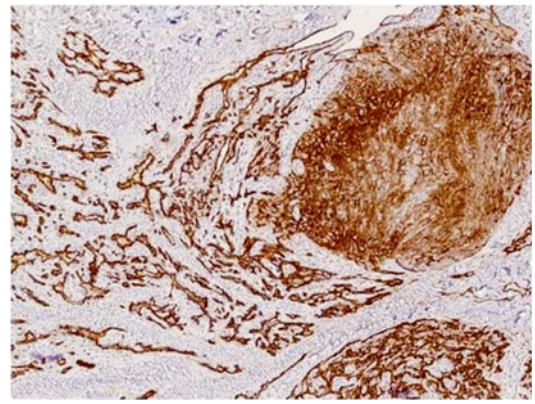

Fig. 38.4 A vascular tumor with mixed features of Dabska's tumor and retiform hemangioendothelioma showing positivity with CD31

Immunohistochemically, the tumor cells react with endothelial markers such as CD31 (Fig. 38.4), CD34, factor VIII-related antigen, and ERG. Staining for CD34 is usually stronger than that for other vascular markers. Claudin-5, a tight-junction protein, has recently been proposed as a reliable vascular marker. Cytokeratins and smooth muscle actin are negative. Most lymphatic markers, including podoplanin (D2-40) and VEGFR-3, are negative. In one case report, HHV8 DNA sequences were claimed to be detected, but in general experience, RH are negative for HHV8.

Differential Diagnosis

The diagnosis is only a histological one. The differential diagnosis prior to biopsy includes lymphoma, dermatofibrosarcoma protuberans, hemangioma, bacillary angiomatosis, cutaneous metastases, blue-rubber bleb nevus syndrome,

Kaposi sarcoma, targetoid hemosiderotic hemangioma (hobnail hemangioma), malignant endovascular papillary angioendothelioma (Dabska's tumor), and cutaneous angiosarcoma. In cases with overlapping features with cutaneous angiosarcoma, the diagnosis is primarily based on the degree of nuclear atypia, the number of mitosis, and the layering of endothelial cells.

Prognosis

It is characterized by a high recurrence rate (60 %) but low metastatic potential. Regional lymph node metastasis has been reported in three cases. To date no patients that developed distant metastasis died from this disease. The existence of soft tissue metastasis is controversial.

Treatment

Treatment of choice is surgical excision. Adjuvant radiotherapy has also been proven effective in cases with lymph node metastasis, large tumor size, or local recurrence.

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Pseudomyogenic Hemangioendothelioma

39

Lauren N Stuart, Jerad M Gardner, and Bruce R Smoller

Introduction

Pseudomyogenic hemangioendothelioma (PH) is an exceedingly rare neoplasm of the skin, soft tissue, and bone with presumed vascular differentiation. Oftentimes, PH is misdiagnosed as epithelioid sarcoma due to shared clinicopathologic features. Distinguishing between these two neoplasms is crucial due to differing therapeutic and prognostic implications.

Clinical Features

PH presents as subcutaneous nodule(s), typically in the distal extremities of young males. The nodules can be painful and involve multiple tissue planes, most commonly the dermis, subcutis, and muscle. Bone destruction and invasion of adjacent structures can occur in advanced disease. When multiple lesions are present, they tend to be grouped within the same anatomic region. The overlying skin may be hyperpigmented or erythematous, although this is not a consistent finding (Fig. 39.1).

Pathology

PH is characterized by an infiltrative proliferation of spindle cells arranged in sheets and fascicles (Figs. 39.2 and 39.3). In some areas, the cells exhibit an epithelioid morphology, with abundant cytoplasm and ill-defined cell borders. Some authors have compared the neoplastic cells to rhabdomyoblasts, due to their glassy and brightly eosinophilic cytoplasm (hence, the name "pseudomyogenic" hemangioendothelioma) (Fig. 39.4). Most cases show mild to moderate cytologic atypia, with few mitoses (<5 per 50 HPF). Other reported features include papillomatous epidermal hyperplasia, ulceration, and increased stromal neutrophils (Fig. 39.5). By immunohistochemistry, the cells are positive for pancytokeratin, CD31, FLI-1, and INI-1 (hSNF5/SMARCB1) (nuclear INI-1 expression retained). Two recent studies have also reported positivity for ERG, further supporting the tumor's presumed vascular origin. CD34, S-100 protein, and desmin are negative. Recently, 3 tumors from a single patient were

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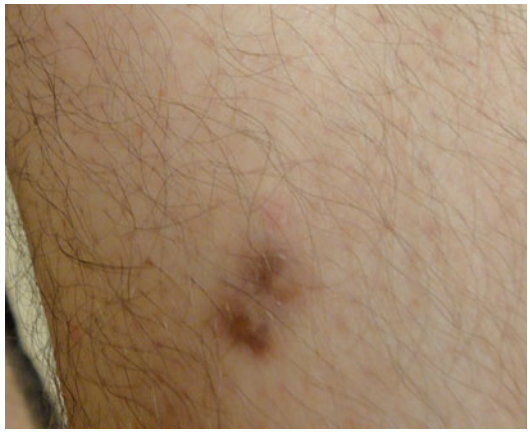

Fig. 39.1 Clinical photo of two adjacent foci of PH from the leg of a young male

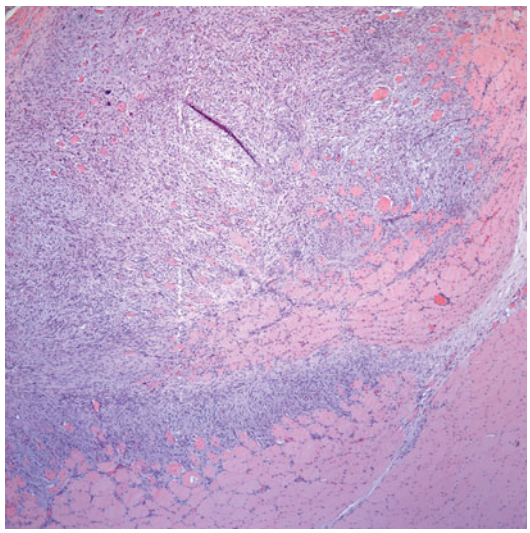

Fig. 39.2 Neoplastic proliferation of spindle cells arranged in sheets and dissecting through the muscle

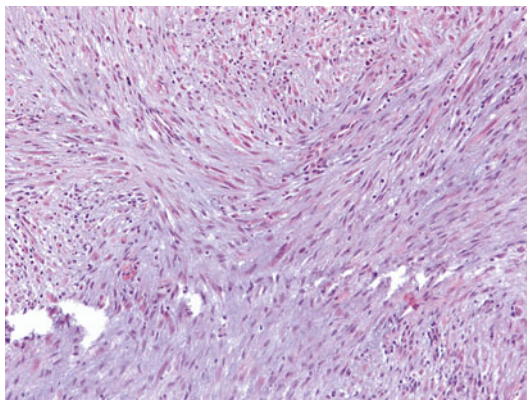

Fig. 39.3 Intersecting fascicles of spindle cells

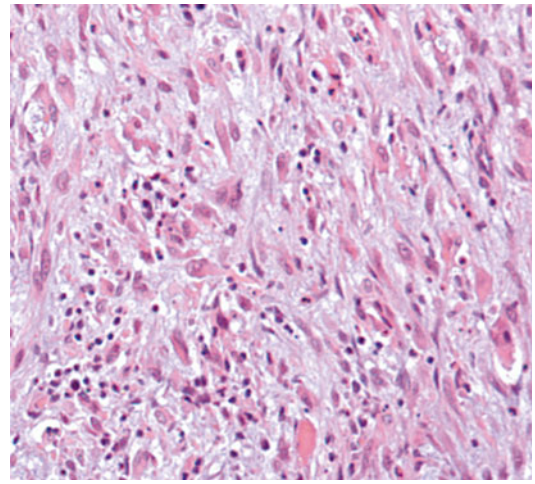

Fig. 39.4 In some areas, the neoplastic cells contain abundant, eosinophilic cytoplasm imparting a rhabdomyoblast-like appearance

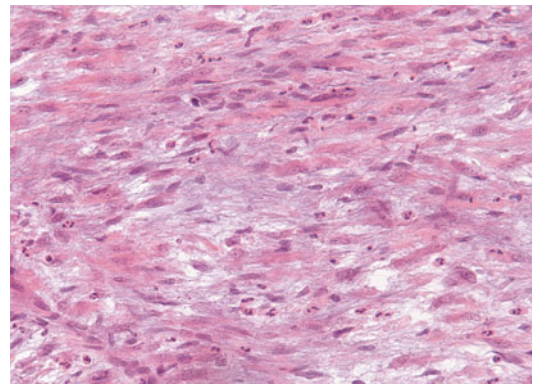

Fig. 39.5 Increased stromal neutrophils are also a common finding

found to harbor a balanced t(7;19)(q22;q13) translocation. In a study of 9 additional cases, an unbalanced der(7)t(1;19) translocation was detected in one case. Further characterization of this genetic anomaly may lead to improved diagnostic accuracy.

Differential Diagnosis

ES, like PH, is a subcutaneous neoplasm with a predilection for the distal extremities of young males. Both tumors are cytokeratin positive and

display epithelioid and spindled cells. However, ES typically exhibits a nodular architecture, as opposed to the infiltrating sheets and fascicles of PH. Moreover, ES is negative for CD31 and displays loss of nuclear INI-1 expression. Other lesions which may be considered include epithelioid angiosarcoma, epithelioid hemangioendothelioma, and cellular fibrous histiocytoma.

Prognosis

PH is classified as a neoplasm of intermediate biological potential, due to its high rate of locoregional recurrence and low risk of distant metastasis. In the largest study to date, recurrence was reported in 58 % of patients, with one patient dying from disease. No other deaths have been reported.

Treatment

While surgical resection is the treatment of choice for most patients, those with multifocal disease may require amputation. Patients with widespread disease may benefit from chemotherapy or postoperative radiation; however, there have been no formal studies investigating the efficacy of these treatments.

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Part VII

Tumours of Fat

Spindle Cell Liposarcoma

40

Elisa Cinotti, Catherine Douchet,
and Franco Rongioletti

Introduction

Spindle cell liposarcoma (SCL) is an uncommon variant of well-differentiated liposarcoma (or atypical lipomatous tumor, adipocytic liposarcoma, lipoma-like liposarcoma). About 20 cases have been reported since the first description in 1994.

Clinical Features

It presents as a painless, slowly enlarging mass, becoming symptomatic when impinging upon surrounding structures; its indolent course can result in a misdiagnosis of cyst or benign soft tissue neoplasm, especially lipoma. It shows predilection for subcutaneous soft tissue of the extremities and orbit. The extraorbital facial locations, neck, vulva, trunk, and palm have also been reported. It tends to occur in adults (range 11–83).

Pathology

It is composed of a spindle cell bland neural-like proliferation arranged in fascicles and whorls set in a fibrous and/or myxoid stroma (Figs. 40.1 and 40.2) and associated with atypical adipocytes (often including lipoblasts) showing variation in size and shape with scattered enlarged and hyperchromatic nuclei (Figs. 40.3 and 40.4). Although grossly liposarcoma is encapsulated, it extends by infiltration. Spindle cells usually exhibit CD34 and adipocytes show S100 protein immunoreactivity.

Incisional biopsy is not indicated in large adipose tumors as malignant degeneration is usually at the center of the mass, and malignant features can be missed, leading to inappropriate treatment.

Genetically, well-differentiated liposarcomas are characterized by the presence of a supernumerary ring or giant chromosomes containing amplified material from chromosome 12q14–q15, which includes the MDM2 and CDK4 genes. However, SCL tends to lack the amplification of MDM2 and/or CDK4, differently from

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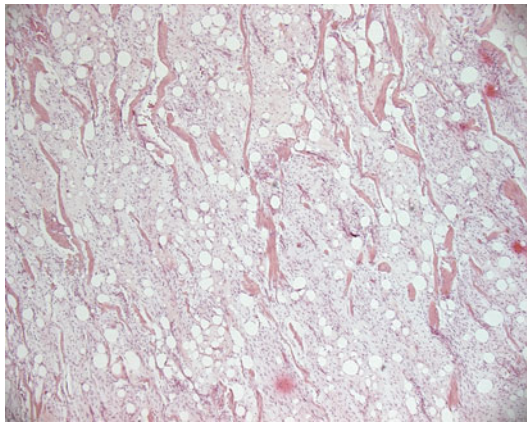

Fig. 40.1 Spindle cell liposarcoma. The neoplasm is composed of a spindle cell bland neural-like proliferation arranged in fascicles and whorls set in a fibromyxoid stroma

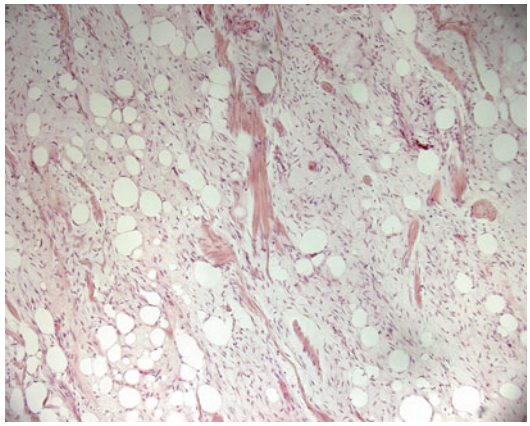

Fig. 40.2 A spindle cell bland neural-like proliferation

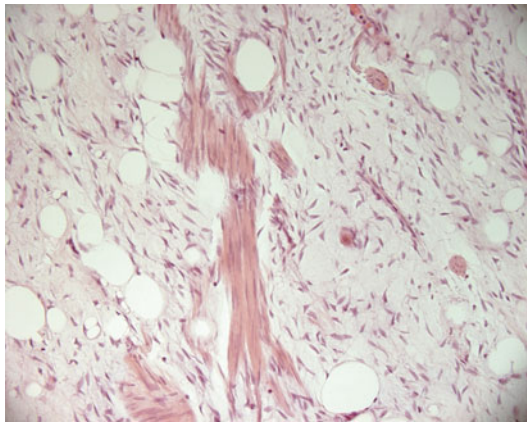

Fig. 40.3 Spindle cells with blunt atypia

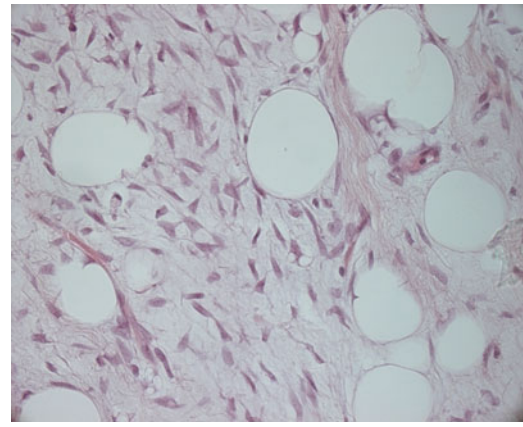

Fig. 40.4 Spindle cells associated with atypical adipocytes and lipoblasts

the other subtypes of well-differentiated liposarcoma. Recently, a partial or complete monosomy of chromosome 7 and a deletion of the Rb-1 gene in the long arm of chromosome 13 without mutations of chromosome 12q region have been identified as other molecular cytogenetic characterization.

Differential Diagnosis

The main differential diagnoses are diffuse spindle cell lipoma (composed of bland, sometimes palisading, CD34-positive spindle cells, admixed with eosinophilic refractile collagen bundles and presenting the Rb-1 deletion) and neurofibroma (characterized by a less cellular S-100-positive spindle cell proliferation with wavy nuclei). Other differential diagnoses are dermatofibrosarcoma protuberans, low-grade malignant peripheral nerve sheath tumor, low-grade sarcoma, low-grade myxofibrosarcoma, dedifferentiated liposarcoma, and the other variants of well-differentiated liposarcoma, such as sclerosing liposarcoma. Low-grade dedifferentiated liposarcoma contains dedifferentiated areas that are generally non-lipogenic, whereas SCL contains well-differentiated atypical adipocytes or lipoblasts, although

sometimes they may dedifferentiate forming non-lipogenic areas.

Prognosis

Mortality seems to be low. The World Health Organization classifies SCL among intermediate (locally aggressive) adipocyte tumors, since local recurrences are quite frequent (around one fourth of patients) and distant metastasis are rare. Prognosis is influenced by adequacy of surgical excision, whereas tumor size and duration of the disease did not appear to be correlated well with prognosis.

Treatment

Surgical removal remains the treatment of choice. The benefit of radiation and chemotherapy remains unproven.

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Myxoid Liposarcoma

41

Irina Margaritescu, A. Doru Chirita, and Florina Vasilescu

Introduction

Liposarcoma represents one of the most common soft tissue sarcomas found in adults. It presents in three main forms: well-differentiated liposarcoma, myxoid/round cell liposarcoma, and pleomorphic liposarcoma. Approximately one third to one half of all liposarcomas are myxoid/round cell liposarcomas. Both myxoid and round cell liposarcomas are often seen as components of the same tumor and show a specific identical genetic abnormality, in the form of translocation t(12;16)(q13;p11). Liposarcoma of all subtypes can occur in the subcutis. However, the dermis seems to represent an exceedingly rare site of occurrence.

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Clinical Features

Myxoid liposarcoma (LPS) presents as a large, slowly growing, deeply located painless mass (Fig. 41.1). The great majority of the lesions occur subfascially, in the intermuscular fascial planes, with a small minority located in the subcutaneous tissue. The lower extremity, in particular the thigh, is the most common affected site. Other sites include the buttocks, trunk, ankle, proximal limb girdle, head and neck, and wrist. The retroperitoneum, abdomen, pelvis, and mediastinum are very rarely involved. Myxoid LPS appears mostly in younger patients, with a peak incidence in the fourth and fifth decades (range 6 months–85 years). Although extremely rare in childhood and adolescence, it represents the most common subtype of LPS in this age group. Males are slightly more affected than females. The tumor size varies between 1.5, and 25 cm and it presents usually as a dome-shaped mass. Extremely rare, it may present as a polypoid tumor. Myxoid LPS may resemble other benign or malignant soft tissue neoplasm that have a soft to only slightly indurated consistency, including skin tags, benign lipomas, atypical lipomatous tumors, low-grade myxofibrosarcomas, and any form of high-grade sarcoma.

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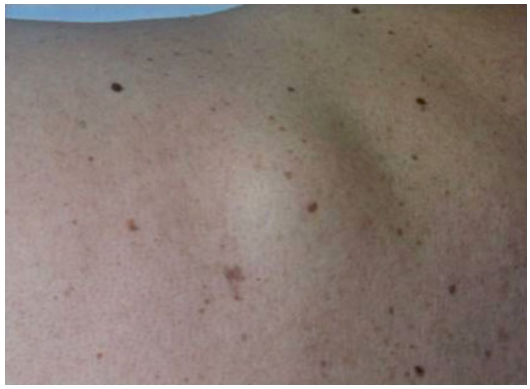

Fig. 41.1 Myxoid liposarcoma. A large, slowly growing, deeply located painless mass on the upper back

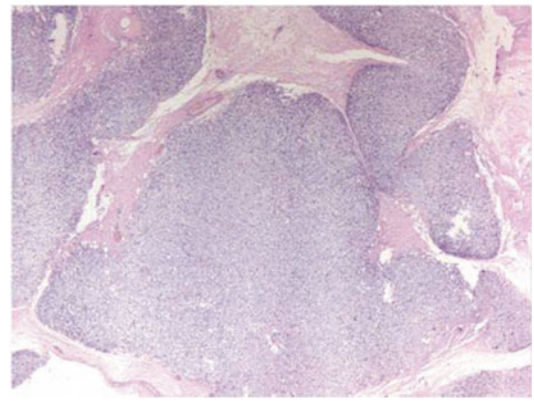

Fig. 41.2 The tumor is composed of well-circumscribed lobulated masses

Pathology

Myxoid LPSs are well circumscribed or encapsulated, lobulated soft tissue tumors (Fig. 41.2). They are composed of a proliferation of small, bland, stellate, spindle-shaped or round cells, with small vacuoles dispersed in a myxoid matrix, giving a pseudolymphangiomatous appearance. A complex plexiform arrangement of small thin-walled capillaries with a chicken wire or crow's feet distribution represents a characteristic feature of myxoid LPS (Fig. 41.3). Multivacuolated lipoblasts are easily identified in the more cellular peripheral regions (Fig. 41.4). Mitoses may be found but are usually sparse. Pleomorphic and multinucleated cells may occasionally be seen. Granular eosinophilic hibernoma-like cells and leiomyomatous, cartilaginous, and osseous metaplasia may occasionally be encountered. Myxoid LPS may present with more cellular areas composed of a variable number of oval-to-round larger cells with hyperchromatic nuclei and inconspicuous cytoplasm (Fig. 41.5). When the round cell population is less than 10 %, the tumor should be regarded as a low-grade liposarcoma. In contrast, when the round cell component predominates, the tumor is associated with a more aggressive behavior (Fig. 41.6). This tumor is known as either combined and round cell LPS or high-grade myxoid LPS. Hemorrhage and/or necrosis may be

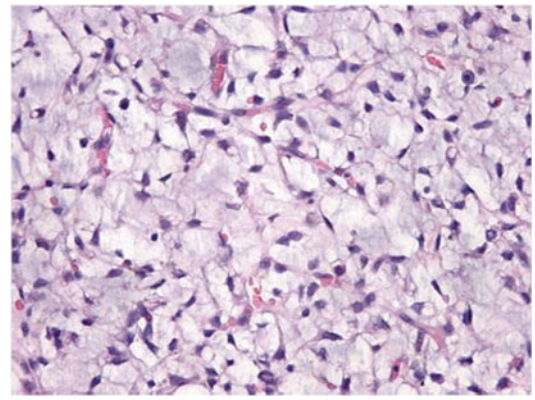

Fig. 41.3 A chicken wire or crow's feet distribution of vessels is a characteristic feature

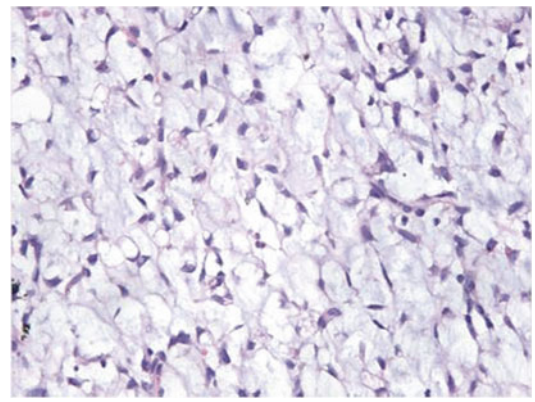

Fig. 41.4 The presence of multivacuolated lipoblasts is an important diagnostic feature

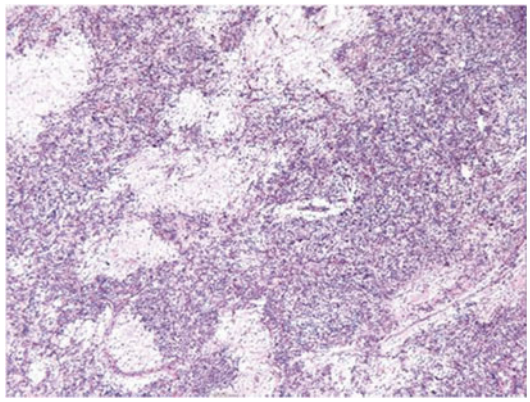

Fig. 41.5 More cellular areas are composed of a variable number of oval-to-round larger cells with hyperchromatic nuclei and inconspicuous cytoplasm

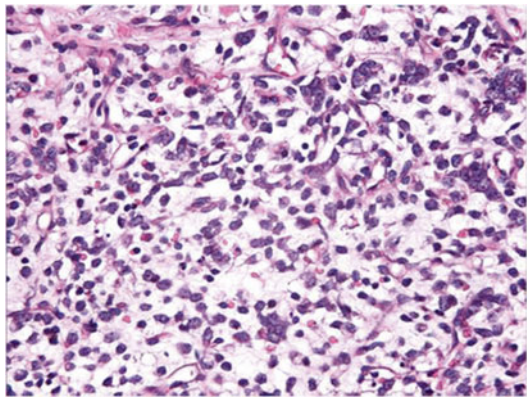

Fig. 41.6 When the round cell component predominates, the tumor is associated with a more aggressive behavior

present in association with high-grade histological features and portend a poor prognosis.

Immunohistochemistry

Myxoid LPS is characterized by a positive reaction for vimentin, desmin, CD34, and S-100 protein. NY-ESO-1 (cancer testis antigen) seems to be a sensitive and a specific marker for myxoid and round cell LPS among mesenchymal myxoid neoplasms.

Molecular studies: Virtually all cases of myxoid and round cell LPS show specific translocations t(12;16)(q13;p11) fusing DDIT3 and FUS. A small subset of cases show t(12;22)(q13;q12) fusing DDIT3 and EWSR1.

Differential Diagnosis

Myxoid LPS should be distinguished from a broad range of benign and malignant neoplasms with myxoid appearance. These include lipoblastoma, well-differentiated liposarcoma with myxoid changes, intramuscular and juxta-articular myxoma, aggressive angiomyxoma, myxoid dermatofibrosarcoma protuberans, myxofibrosarcoma, and myxoid chondrosarcoma. Appropriate immunohistochemistry using a large panel of antibodies coupled with molecular and ultrastructural studies and a careful clinicopathologic correlation allows for the correct diagnosis in each and every case.

Prognosis

Myxoid liposarcoma has a high risk for local recurrence and distant metastasis. The local recurrence and distant metastasis rate is approximately 13–33 % and 11 %, respectively. The prognostic factors associated with a poor prognosis are: age (>45 years), large tumor size (≥10 cm), high histological grade (≥5 % round cell component), presence of tumor necrosis, and p53 overexpression. The tumor size, histological grade, and initiation of chemotherapy are factors that influence the pattern of metastases. Thus, large tumor size and low histological grade are significantly associated with extrapulmonary metastasis (retroperitoneal, pericardial, subcutaneous, and osseous). Low-grade myxoid LPS has a 5- and 10-year disease-specific survival rates of 90 % and 77 %, respectively.

Treatment

A complete resection of the neoplasm with wide surgical margins represents the treatment of choice for myxoid LPS. Although radiotherapy seems to have no impact on either overall or disease-free survival, it can be used to decrease

the risk of local recurrence in cases with close or positive surgical margins. The role of chemotherapy remains unclear. Trabectedin (ecteinascidin-743) may be of some benefit in this tumor type (approximately 50 % of patients showed a partial clinical response in a recent study).

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Part VIII

Tumours of Muscle

Cutaneous Leiomyosarcoma

42

Franco Rongioletti

Introduction

Cutaneous leiomyosarcoma accounts for 7 % of all soft tissue sarcomas. The primary cutaneous leiomyosarcoma may be subdivided into two types: superficial (or dermal) leiomyosarcoma and subcutaneous (or deep) leiomyosarcoma. The superficial (dermal) leiomyosarcoma does not exceed 3 % of all sarcomas and will be the main topic of this chapter. As superficial leiomyosarcoma is remarkable for its good prognosis in contrast to its deeper counterpart, the name of "atypical intradermal smooth muscle neoplasm" has been suggested instead of cutaneous leiomyosarcoma.

Clinical Features

Superficial (dermal) leiomyosarcoma originates from the arrector pili muscles or genital dartoric muscles and presents as solitary, slow-growing erythematous to brownish nodule of 0.5–3 cm in diameter when first detected, predominantly located on the lower extremities (50 ~ 75 %) (Fig. 42.1) and the trunk. Most case series report a predilection for middle-aged to elderly Caucasian males (50–70 years). Subcutaneous leiomyosarcoma originates from the smooth muscles of blood vessels and presents as a larger movable mass in the subcutis without epidermal change. In both variants, spontaneous pain or tenderness may be present. Trauma, radiation, chemicals, scars, and sunlight have considered as the main predisposing triggers. Malignant transformation from a leiomyoma may occur.

The familial occurrence of cutaneous leiomyosarcoma with renal cancer has been described in the context of hereditary cutaneous leiomyomatosis and renal cell cancer (HLRCC). This rare genetic syndrome is caused by heterozygous mutations in the fumarate hydratase (FH) gene.

Pathology

Superficial (dermal) leiomyosarcoma is confined to the dermis or showed only very superficial, focal subcutaneous extension. The neoplasm is characterized by a poorly circumscribed proliferation of interwoven fascicles of spindle-shaped atypical myomatous cells with eosinophilic cytoplasm and cigar-shaped nuclei that merge with a collagenous stroma (Figs. 42.2 and 42.3). Mitotic figures (1/2 per 10 high-power fields), high cellularity, and bizarre myomatous cells are the generally accepted criteria for malignancy (Fig. 42.4). Two growth patterns are described: a

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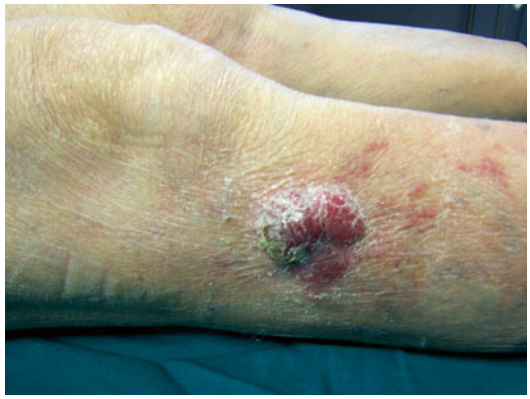

Fig. 42.1 Cutaneous leiomyosarcoma. A slow-growing erythematous to brownish nodule of 5 cm in diameter on the leg

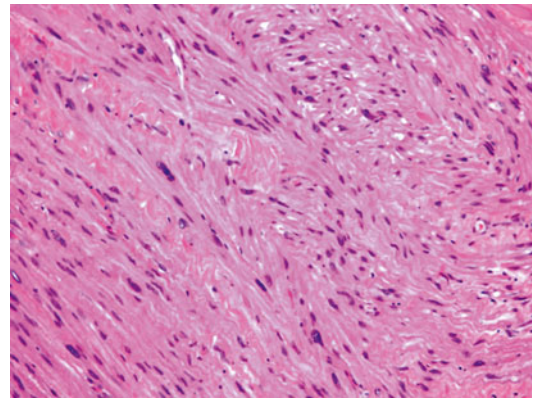

Fig. 42.4 Mitotic figures, high cellularity, and bizarre myomatous cells

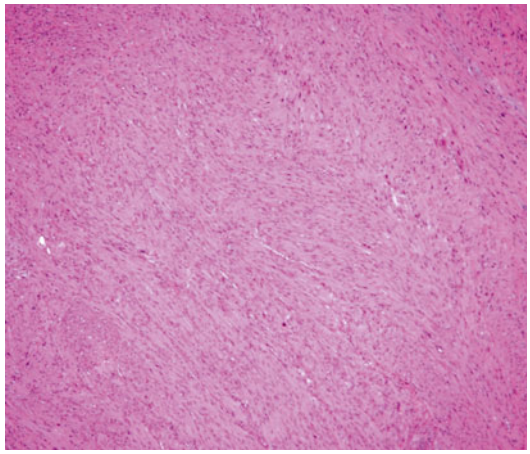

Fig. 42.2 A poorly circumscribed proliferation of interwoven fascicles of spindle-shaped atypical myomatous cells that merge with a collagenous stroma

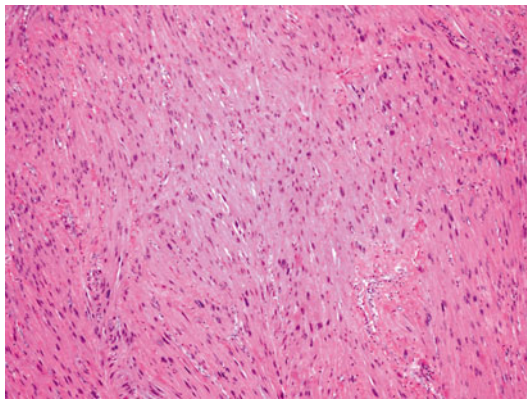

Fig. 42.3 The cells show an eosinophilic cytoplasm and cigar-shaped nuclei

nodular pattern characterized by high cellularity, marked nuclear atypia, and numerous mitoses and a diffuse pattern that is less cellular and well differentiated and shows inconspicuous mitoses. Focal areas of hemorrhage with necrosis and inflammatory component are present. Unusual histological variants include epithelioid, granular cell, inflammatory, myxoid, and desmoplastic leiomyosarcoma. α-smooth muscle actin (α-SMA), muscle actin specific (HHF35), and calponin and caldesmon staining are positive in a vast majority of cases (Fig. 42.5a, b). However, none of these markers is absolutely specific for smooth muscle, and positivity for at least two of these markers is more supportive of leiomyosarcoma. Desmin is positive in 50–70 % of cases. MIB-1 labeling index can be useful as adjunctive aids for recognizing malignancy. Focal positivity for cytokeratins, EMA, CD34, and S-100 protein may be encountered. Although a loss of PTEN acting as a tumor suppressor gene has been reported in a case series, its significance in tumor genesis and its diagnostic utility remain to be determined.

Differential Diagnosis

Histological findings may lead to confusion with other atypical cutaneous spindle cell tumors such as atypical fibroxanthoma, dermatofibrosarcoma protuberans, angiosarcoma, and spindle cell

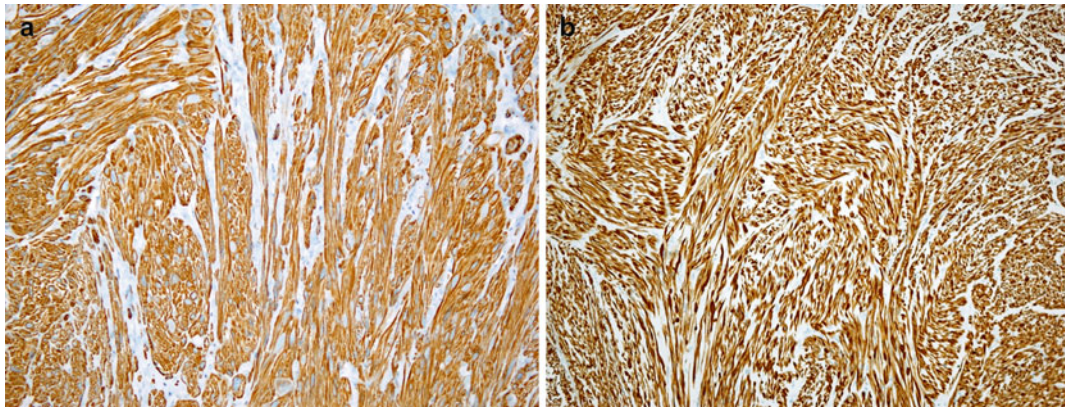

Fig. 42.5 (**a**) α-smooth muscle actin (α-SMA) and (**b**) desmin positivity

squamous cell carcinoma. Immunohistochemistry, especially with actin markers, is mandatory in arriving at a definitive diagnosis.

Prognosis

Superficial (dermal) leiomyosarcoma has a better prognosis than subcutaneous leiomyosarcoma. While the former shows local recurrence rates of 30–50 % and rarely metastasizes, the latter recurs up to 70 %. The metastatic potential is 5–10 % for the dermal form compared with 30–60 % for the subcutaneous form. Complete surgical resection is considered to be the most important factor influencing the prognosis in patients with both superficial and deep leiomyosarcoma. Several poor prognostic factors include tumor size ≥5 cm, acral distribution, deep localization with fascia involvement, and high malignancy grade. The clinical behavior of purely dermal superficial leiomyosarcoma is different from that of superficial leiomyosarcoma with minimal subcutis invasion, the latter being associated with higher rate of local recurrences (18.1 % vs. 6 %) and/or distant metastases.

Treatment

Treatment of superficial leiomyosarcomas consists mainly of early wide local excision including a 2 ~ 5 cm excision margin with a depth including the subcutaneous tissue. A surgical intervention with inadequate margins places the patient at high risk for local recurrence and metastatic disease, especially in case of a subcutaneous leiomyosarcoma. The role of radiotherapy and adjuvant chemotherapy in superficial leiomyosarcoma is controversial and seems that the neoplasm is radio- and chemoresistant. These modalities should be reserved for tumors larger than 5 cm and for high-grade tumors in order to reduce the likelihood of relapses and in combination with surgery in cases of recurrent tumors. Mohs micrographic surgery has been used in the management of superficial leiomyosarcomas with a reported recurrence rate of 0–14 %.

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Primary Cutaneous Rhabdomyosarcoma

43

Jerad M. Gardner and Bruce R. Smoller

Introduction

Rhabdomyosarcoma is a malignant mesenchymal neoplasm with skeletal muscle differentiation that typically occurs in the deep soft tissue or viscera. Three subtypes comprise the majority of cases of rhabdomyosarcoma: embryonal, alveolar, and pleomorphic. All three types may very rarely occur as primary tumors arising in the skin or subcutis without deep soft tissue involvement. Other uncommon subtypes, such as epithelioid rhabdomyosarcoma, also exist and may occur in the skin, as well. Less than 50 cases of primary cutaneous rhabdomyosarcoma (PC-RMS) have been reported.

Clinical Features

These tumors present mostly on the head and neck or extremities, although the trunk and other sites may also be involved. The clinical appearance is varied and nondescript. Proposed clinical diagnoses in some of the reported cases have included keloid, cyst, hematoma, sarcoidosis, dermatofibroma, and basal cell carcinoma among others. PC-RMS has a bimodal age distribution similar to conventional rhabdomyosarcoma with children (approximately 2/3) and elderly adults (approximately 1/3) being the most commonly afflicted. Children with PC-RMS are more likely to have alveolar and embryonal subtypes, while adults more commonly have the pleomorphic or epithelioid subtype according to one series (J Cutan Pathol 2012: 39: 987–995). Unlike conventional RMS which has a slight male predominance, there appears to be a slight female predominance in PC-RMS.

Pathology

By definition, the tumor must be confined to the dermis, subcutis, or both without involvement of deep soft tissue (Figs. 43.1 and 43.2). However, PC-RMS occurring on the face may extend into the superficial skeletal muscle of the dermis. The histological features are dependent upon the subtype. The alveolar subtype is composed of aggregates of monotonous round cells divided by thick fibrous septa; central discohesion of tumor cells may be seen giving an "alveolar" appearance (Figs. 43.3 and 43.4). The embryonal subtype displays hyperchromatic ovoid cells arranged in sheets with alternating cellularity and a myxoid background; scattered rhabdo-

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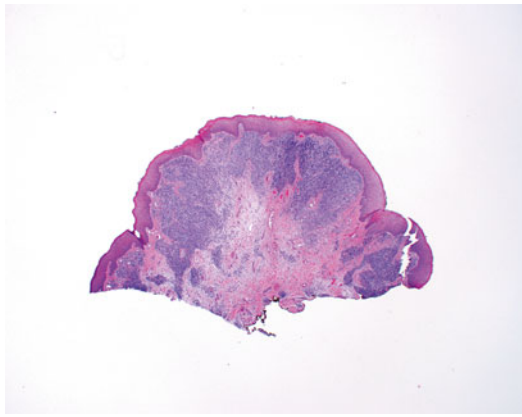

Fig. 43.1 PC-RMS is a multinodular proliferation of atypical round or spindle cells centered in the dermis and/or subcutis

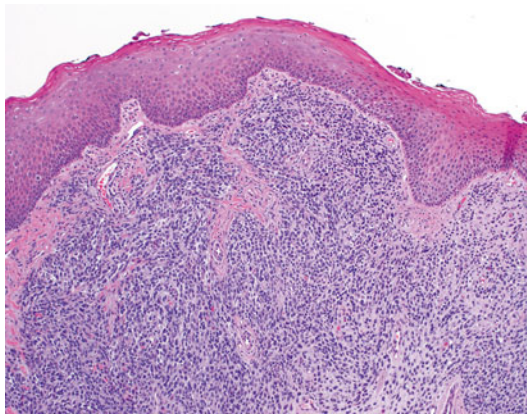

Fig. 43.2 The tumor cells are arranged in nodules and sheets without epidermal involvement

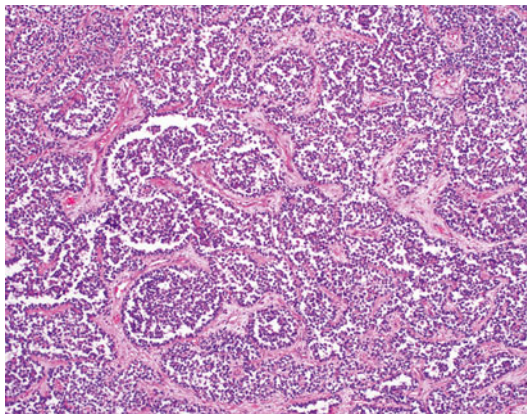

Fig. 43.3 The alveolar subtype is composed of aggregates of "small round blue" cells divided by thick fibrous septa. Central discohesion of tumor cells is often present resulting in an "alveolar" appearance

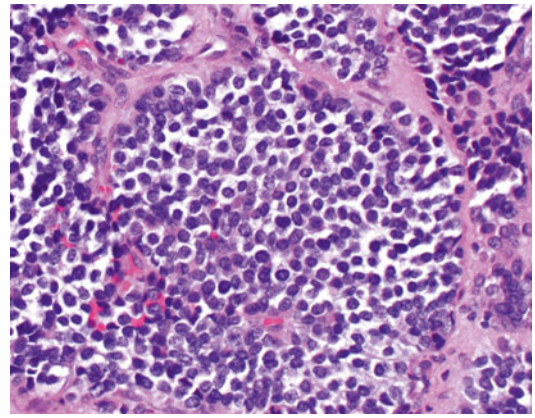

Fig. 43.4 In the alveolar subtype, the tumor nuclei are relatively uniform and monotonous

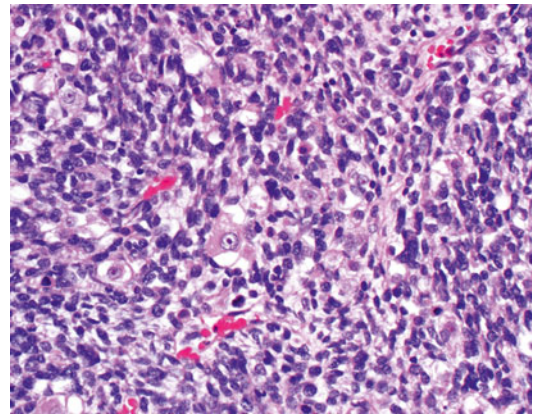

Fig. 43.5 The embryonal subtype displays hyperchromatic ovoid cells admixed with scattered rhabdomyoblasts with abundant eosinophilic cytoplasm

myoblasts with abundant eosinophilic cytoplasm are usually seen (Fig. 43.5). The pleomorphic subtype is composed of sheets of pleomorphic spindled rhabdomyoblasts characterized by eccentrically located atypical nuclei and abundant dense eosinophilic cytoplasm (Fig. 43.6). The epithelioid subtype is composed of pleomorphic round epithelioid cells with abundant dense eosinophilic cytoplasm (Fig. 43.7). The tumor cells express strong diffuse desmin (Fig. 43.8) and also show nuclear expression of myogenin (Fig. 43.9) and/or MYOD1, both of which are highly specific markers of skeletal muscle differentiation. Focal cytokeratin expression may also be seen. Smooth muscle actin is

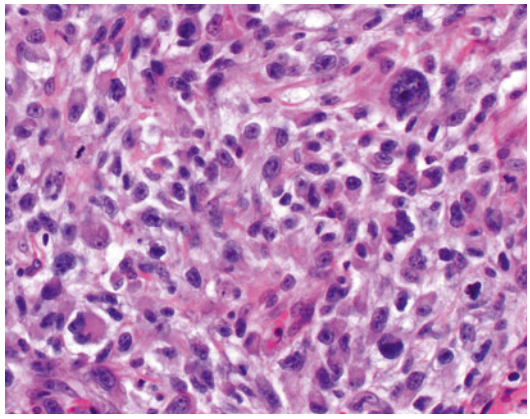

Fig. 43.6 The pleomorphic subtype is composed of sheets of pleomorphic spindle cells, some of which have eccentrically located atypical nuclei and abundant dense eosinophilic cytoplasm

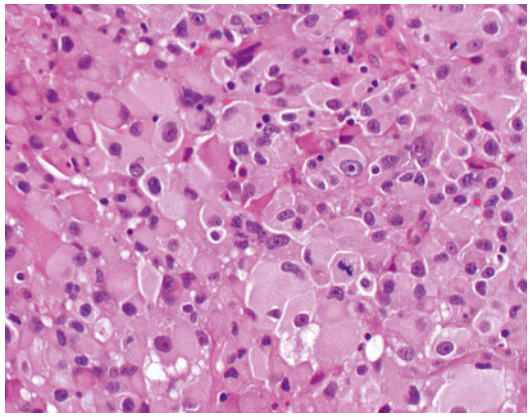

Fig. 43.7 The epithelioid subtype is composed of pleomorphic round epithelioid cells with abundant dense eosinophilic cytoplasm

typically negative. The alveolar subtype may show rearrangement of the FOX01A gene by either FISH or RT-PCR.

Differential Diagnosis

The most important differential diagnoses to exclude are cutaneous metastasis of rhabdomyosarcoma and cutaneous extension of a deep soft tissue rhabdomyosarcoma; both require clinical correlation. Additionally, the histological differential diagnosis for PC-RMS is quite broad. The alveolar subtype may be confused with other

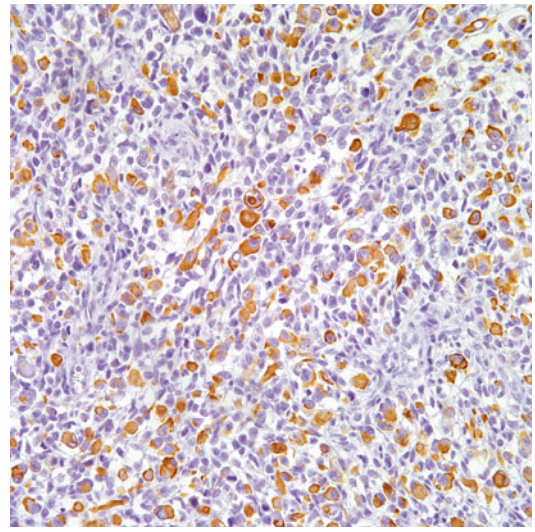

Fig. 43.8 Focal or diffuse cytoplasmic expression of desmin is virtually always present in PC-RMS (embryonal subtype)

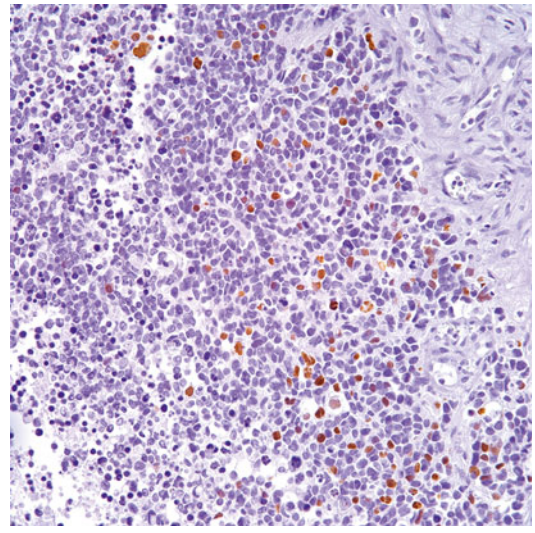

Fig. 43.9 Nuclear expression of myogenin is a highly sensitive and specific marker of PC-RMS (embryonal subtype)

"small round blue cell" tumors including Ewing's sarcoma/primitive neuroectodermal tumor, metastatic neuroblastoma, hematopoietic malignancies, Merkel cell carcinoma (in adults), and metastatic small cell carcinoma (in adults). The embryonal subtype may superficially resemble leukemia cutis. For the pleomorphic subtype, the histological differential diagnosis includes

atypical fibroxanthoma, superficial undifferentiated pleomorphic sarcoma, sarcomatoid or poorly differentiated squamous cell carcinoma, metastatic carcinoma, melanoma, proximal-type epithelioid sarcoma, epithelioid angiosarcoma, myoepithelial carcinoma, and high-grade synovial sarcoma. The use of immunohistochemistry will serve to make these distinctions in the vast majority of cases.

Prognosis

Just like its deep counterpart, PC-RMS is an aggressive neoplasm that may yield distant metastases, usually to the lung. It has a 36 % mortality rate according to the largest published series.

Treatment

As this is a very rare tumor, there is no standardized treatment for PC-RMS. It is often treated by surgical excision usually coupled with chemotherapy and/or radiotherapy. Some children with PC-RMS have been treated according to the rhabdomyosarcoma-specific treatment protocols that are utilized in conventional pediatric rhabdomyosarcoma.

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Malignant Rhabdoid Tumor

44

Elisa Cinotti and Franco Rongioletti

Introduction

Malignant rhabdoid tumor (MRT) was originally described by Haas et al. in 1981 as an aggressive childhood renal tumor that was believed to represent a rhabdomyosarcomatous variant of Wilms tumor (or nephroblastoma). MRT was later recognized as a separate entity, and extrarenal rhabdoid tumors occurring in various sites such as the brain (atypical tattooed rhabdoid tumor), spinal dura, lung, liver, colon, esophagus, ovary, uterus, vulva, bladder, skin, and soft tissue have been reported. Moreover, it was shown that although MRT cells were similar to rhabdomyoblasts, they were not related to myogen cells, and they were negative for muscle cell markers.

The rhabdoid phenotype has emerged in cutaneous neoplasms, either as a pure extrarenal rhabdoid tumor or a composite phenotype coupled with another malignancy such as melanoma or squamous cell carcinoma. Controversy exists as to whether the MRT is a distinct clinicopathologic entity or merely a shared phenotypic expression of histogenetically divergent tumors. In fact, rhabdoid features may represent a common dedifferentiated end point for a variety of neoplasms, and they may be regarded as a phenotype.

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Clinical Features

Cutaneous malignant rhabdoid tumor is usually metastatic from renal or soft tissue primary tumors (mostly retroperitoneal tumors). Primary cutaneous MRT is extremely rare and mostly occurs in patients less than 1 year of age (mean age 2.9 years). Only about 21 cases of primary cutaneous MRT in adults have been reported. The clinical features are not diagnostic consisting of deep masses with a predominant involvement of the neck or paraspinal region in infants. Sometimes, the lesion may be hypervascular, mimicking a hemangioma. In adults, deep nodules that may ulcerate have been described.

Pathology

Rhabdoid features are defined by morphological characteristics such as large round cells with abundant pale eosinophilic cytoplasm containing

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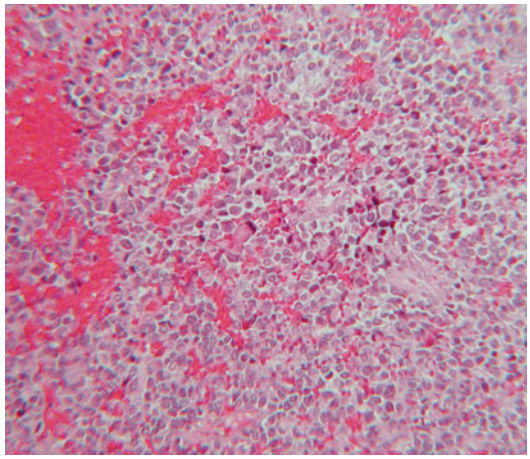

Fig. 44.1 Malignant rhabdoid tumor. Rhabdoid, large round cells with abundant pale eosinophilic cytoplasm containing hyaline filamentous inclusions, eccentric nuclei, and large prominent nucleoli

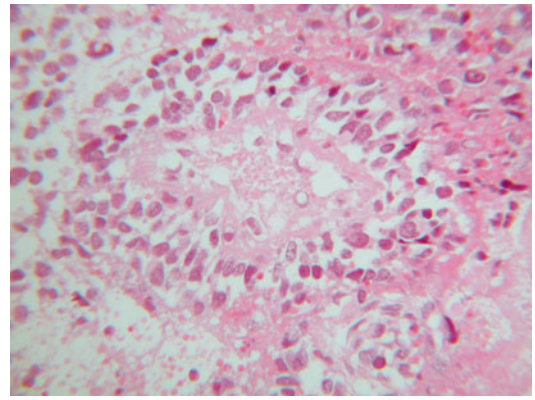

Fig. 44.3 Malignant rhabdoid tumor. Areas of necrosis are present

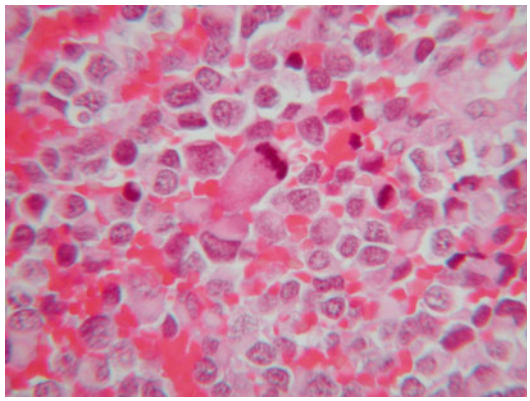

Fig. 44.2 Malignant rhabdoid tumor. Mitotic activity is prominent

hyaline filamentous inclusions, eccentric nuclei, and large prominent nucleoli (Figs. 44.1 and 44.2). Mitotic figures are abundant and areas of necrosis are usually seen (Fig. 44.3).

Rhabdoid tumors are often positive for vimentin (>90 %) (Fig. 44.4a), epithelial membrane antigen (EMA) (80 %), and AE1/AE37 (80 %) and can show focal expression of glial fibrillary acidic protein (GFAP), desmin, S-100, neuron-specific enolase (NSE), and actin (Fig. 44.4b). Moreover, 90 % of tumors lack the normal nuclear immunohistochemical expression of the protein INI1 (SMARCB1 or SWI-SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1) derived from the inactivation of *hSNF5/INI-1* tumor suppressor gene (22q11.2). On electron microscopy, the tumor cells show a cytoplasmic paranuclear whorl of intermediate filaments containing an entrapped rough endoplasmic reticulum, mitochondria, and lipids.

Differential Diagnosis

The lack of expression of the leukocyte common antigen (LCA), Wilms tumor 1 (WT1), and NSE allow to rule lymphoma, Wilms tumor, and neuroblastoma. Rhabdoid morphology has been described in squamous cell carcinomas, but lack of expression of both high- and low-molecular-weight cytokeratins excludes an epithelial neoplasm. Moreover, rhabdoid phenotype has been demonstrated in conjunction with epithelioid malignant peripheral nerve sheath tumors, rhabdomyosarco-

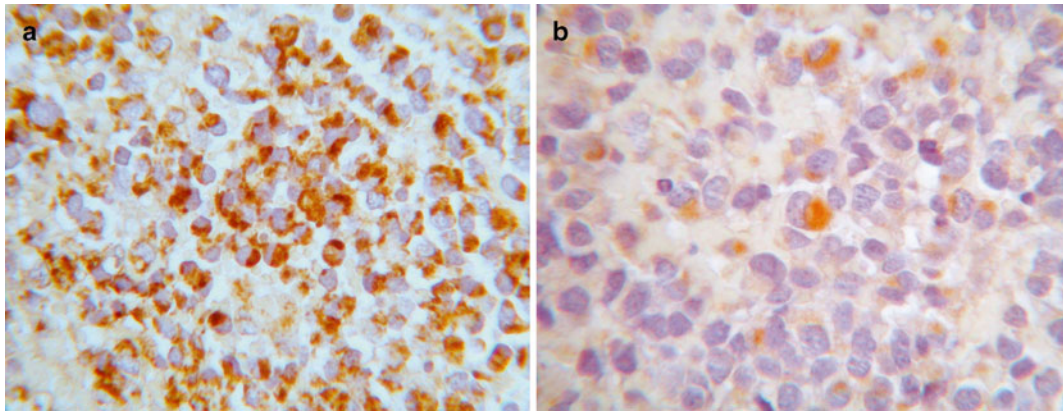

Fig. 44.4 Malignant rhabdoid tumor. (**a**) Rhabdoid cells are positive for vimentin and (**b**) focally for actin

mas, and melanomas. Rhabdomyosarcoma can be diagnosed if markers for striated muscles (MSA, myogenin, MyoD1) are present.

Prognosis

Renal and extrarenal MRT are aggressive, with widespread metastatic disease including blood borne and central nerve system infiltration. Prognosis is extremely poor.

Treatment

Early wide surgical excision of the tumor is the treatment of choice. In addition, chemotherapy (ifosfamide, actinomycin-D, vincristine, carboplatin, and epirubicin) is recommended, but the best regime is not yet defined. No unequivocal policy is in place with regard to radiotherapy, but recent reports indicate that it is a useful adjuvant treatment.

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Part IX

Tumours of Bone

Primary Cutaneous Extraskeletal Osteosarcoma

45

Jerad M. Gardner and Bruce R. Smoller

Introduction

Osteosarcoma is a malignant bone-producing neoplasm that typically occurs in the long bones of adolescents and young adults. Extraskeletal osteosarcoma (EO) is a rare variant of osteosarcoma that usually arises in the deep soft tissue, most commonly of the lower extremities, and accounts for 1–2 % of all osteosarcomas. These may rarely be confined to the skin where they are referred to as primary cutaneous extraskeletal osteosarcoma (PC-EO). Most examples of PC-EO in the literature are either single case reports or are combined into case series with EO of deep soft tissue.

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Clinical Features

Unlike osteosarcoma of the bone, EO and PC-EO more commonly arise in adults over the age of 30. PC-EO usually presents as a nondescript skin nodule or exophytic mass. A history of previous local radiation or trauma is present in a minority of cases but most appear to arise de novo.

Pathology

By definition, the tumor must be confined to the dermis, subcutis, or both without involvement of deep soft tissue. It typically displays sheets of pleomorphic spindle cells involving the dermis and/or subcutis (Fig. 45.1). Osteoid production, the sine qua non for the diagnosis of osteosarcoma, may be diffuse or focal and limited to the center of the tumor (Figs. 45.2 and 45.3). Strands of dense eosinophilic osteoid are usually closely associated with the tumor cells causing individual cells to become encased in osteoid (Figs. 45.4 and 45.5). The osteoid often shows areas of granular basophilic or purple calcification (Figs. 45.1, 45.2 and 45.3). Although specific immunohistochemical markers for osteosarcoma are not available, it is typically negative for cytokeratins and melanocytic markers. Thus, immunohistochemistry may be useful to exclude other entities in the differential diagnosis that may show ossification such as melanoma, melanocytic nevi, carcinomas

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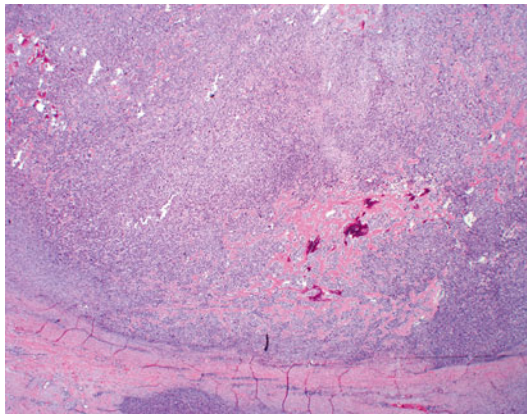

Fig. 45.1 PC-EO displays sheets of hyperchromatic spindle cells with an intervening network of densely eosinophilic osteoid which shows focal calcification

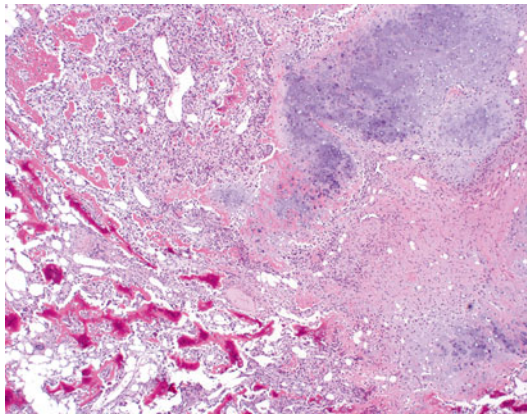

Fig. 45.2 In addition to osteoid production, cartilaginous differentiation may also be seen in PC-EO

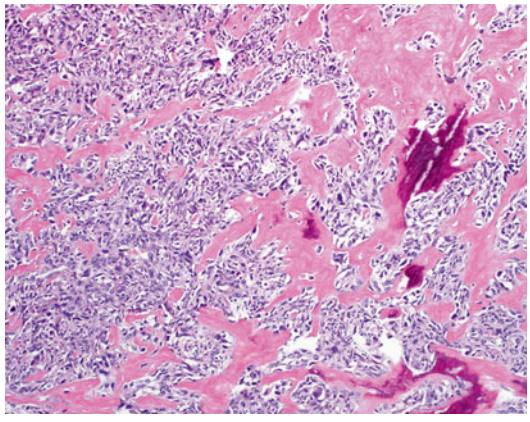

Fig. 45.3 Markedly atypical spindle cells intimately associated with strands of densely eosinophilic osteoid are the hallmark of PC-EO. The presence of purple/basophilic calcification is useful in confirming the presence of true osteoid

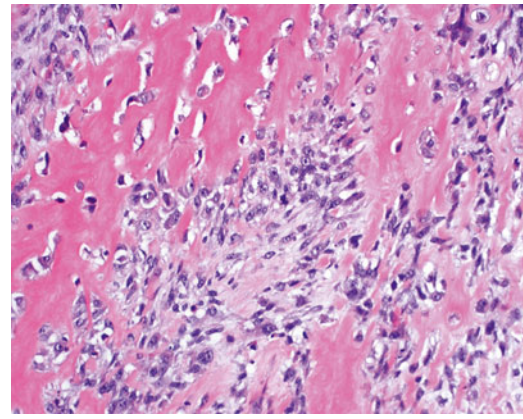

Fig. 45.4 Atypical tumor cells are often entrapped within the osteoid in PC-EO

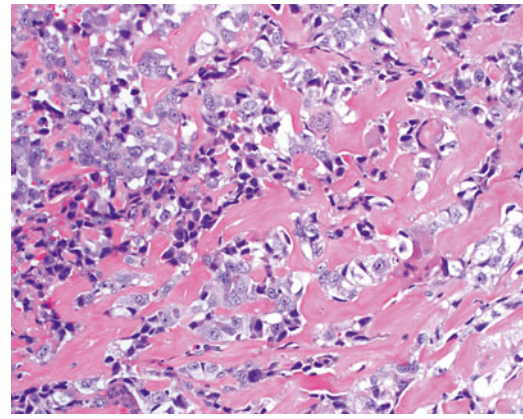

Fig. 45.5 Atypical tumor cells are often entrapped within the osteoid in PC-EO. Strands of osteoid are seen between individual tumor cells

of various etiologies, ossifying fibromyxoid tumor of soft parts, and a range of keratin-producing adnexal tumors.

Differential Diagnosis

The most important differential diagnoses to exclude are cutaneous metastasis of osteosarcoma and cutaneous extension of a deep osteosarcoma of bone or deep soft tissue; both require clinical and radiographic correlation. Matrix producing melanoma may closely mimic extraskeletal osteosarcoma, and osteosarcomatous transformation can rarely be seen in sarcomatoid carcinoma, but

both of these possibilities can typically be excluded by immunohistochemistry. Other benign and malignant skin tumors and reactive processes may sometimes display metaplastic ossification, a reactive phenomenon which may lead to confusion with osteosarcoma. Unlike the fine strands of osteoid intimately associated with malignant tumor cells that typify osteosarcoma, metaplastic ossification is usually a well-differentiated osteoid similar to mature bone. Metaplastic ossification is a typical feature of myositis ossificans, ossifying fibromyxoid tumor of soft parts, and osteoma cutis. It can also be seen as a secondary finding in a wide variety of benign and malignant neoplasms including pilomatricoma, intradermal nevus, desmoplastic melanoma, basal cell carcinoma, dermatofibroma, chondroid syringoma (mixed tumor), melanoma, and other sarcomas.

Prognosis

Deep EO has a poor prognosis with a mortality of over 60 % in one study, but the prognosis of PC-EO is more difficult to determine as no case series exists. Tumor size of less than 5 cm and ability to obtain complete resection, both features that may be more likely in PC-EO, are thought to indicate a somewhat better prognosis. However, distant metastasis and death have been reported in PC-EO. Metastases of PC-EO usually present in the lungs, but the liver and even regional lymph nodes have been reportedly involved.

Treatment

As this is a very rare tumor, there is no standardized treatment for PC-EO or its deep soft tissue counterpart. It is often treated by surgical excision sometimes coupled with chemotherapy and/or radiotherapy.

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Part X

Melanocytic Tumours

Desmoplastic Melanoma

46

Irina Margaritescu and A. Doru Chirita

Introduction

First described by Conley et al. in 1971, desmoplastic melanoma (DM) represents a distinctive rare variant of spindle cell melanoma that usually develops on chronically sun-damaged skin in older people and has a tendency for local recurrence.

Clinical Features

It presents especially in the elderly with a predilection for sun-exposed areas, but the tumor may be present at any age. The head and neck region is the most common site involved, representing more than half of the cases, followed by the upper limbs, thorax, and lower limbs. The lip, palate, nasal vestibule, conjunctiva, and genitalia may also be affected. As the clinical presentation is often nonspecific (amelanotic nodule, ill-defined indurated scar-like plaque) and the tumor may resemble a benign lesion (cyst, dermatofibroma, hypertrophic or keloid scar), the correct diagnosis is usually delayed. As a consequence, the tumors are deeply infiltrative by the time of diagnosis. However, some tumors have a more obvious superficial component of melanoma that aids the diagnosis (Fig. 46.1). Recurrent lesions usually present as painful and indurated subcutaneous nodules in or near the scar from previous excision (Fig. 46.2).

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Pathology

The tumor is characterized by a diffusely infiltrative spindle cell proliferation arranged in poorly formed fascicles accompanied by marked interstitial fibrosis and punctuated by collections of lymphocytes (Figs. 46.3 and 46.4). The poorly demarcated neoplasm usually involves the whole dermis, and it frequently extends into the subcutaneous fat. Involvement of skeletal muscle or underlying bone can be found at the time of diagnosis. Nerve involvement is a commonly associated feature and sometimes it may be very marked in the neurotropic variant of DM.

The melanocytes are nonpigmented spindle cells and usually have a bland appearance with slightly pleomorphic and hyperchromatic nuclei, inconspicuous nucleoli, and low mitotic activity (Fig. 46.5). However, at least in some foci, there are cells with higher degree of cytologic atypia (Fig. 46.6). Based on the degree of desmoplasia and cellularity, DM has been classified by Busam et al. into two histopathologic subtypes. The pure

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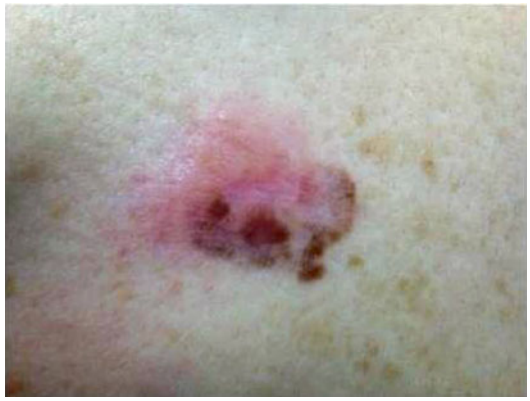

Fig. 46.1 Desmoplastic melanoma. An ill-defined indurated plaque on the back of a 60-year-old female. Pigmentation and signs of regression suggest the diagnosis

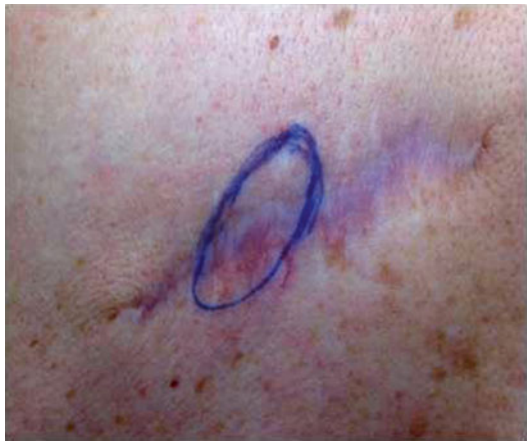

Fig. 46.2 Desmoplastic melanoma. A painful and indurated subcutaneous nodule in or near the scar from previous excision usually represents a sign of recurrence

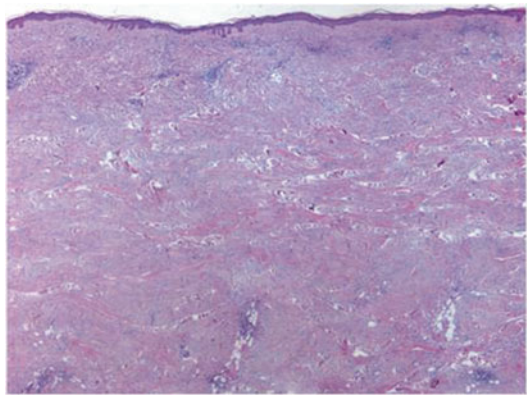

Fig. 46.3 Desmoplastic melanoma is often a deeply infiltrative tumor at presentation

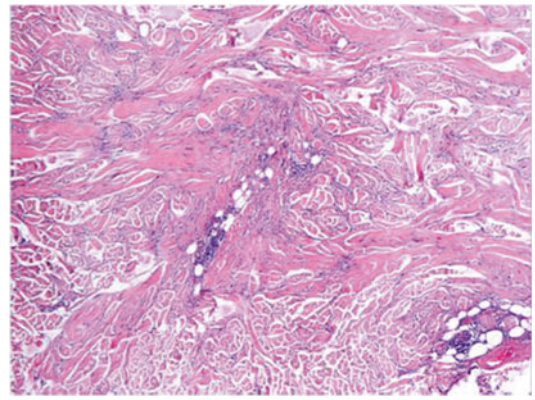

Fig. 46.4 The tumor is characterized by a spindle cell proliferation arranged in poorly formed fascicles accompanied by marked interstitial fibrosis and punctuated by collections of lymphocytes

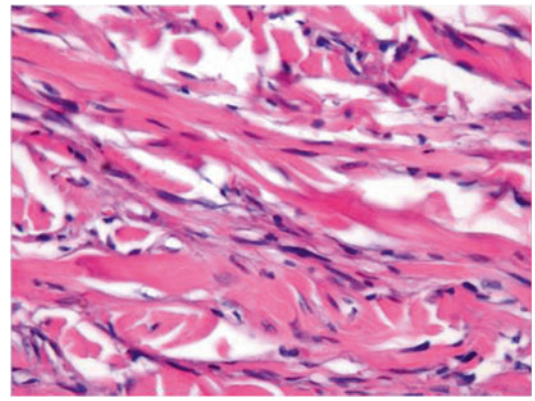

Fig. 46.5 The neoplasm is often deceptively bland in appearance

variant (pDM) is typically paucicellular and has prominent desmoplasia. The mixed type (mDM) is more cellular than pDM and comprised of areas of conventional melanoma in a background of classic paucicellular DM. Early recurrent tumors are frequently paucicellular and may be difficult to distinguish from scar tissue. The overlying epidermis may show features of melanoma "in situ" or of a melanoma with underlying regression, but in many cases, no such in situ changes are detected (Figs. 46.7 and 46.8).

Immunohistochemically, DM expresses S-100 protein, NSE (neuron-specific enolase), vimentin, NKI/C3 (CD63), and p75NGF-R (nerve growth

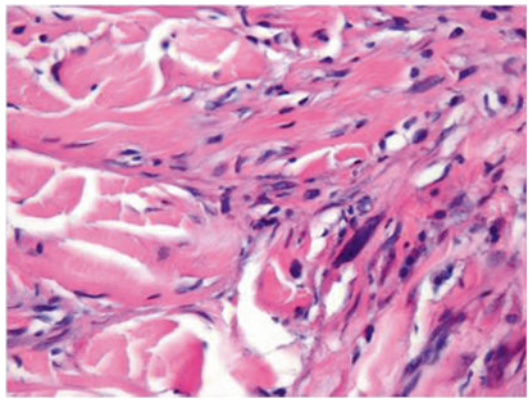

Fig. 46.6 In some foci, cells with big hyperchromatic and pleomorphic nuclei can be found

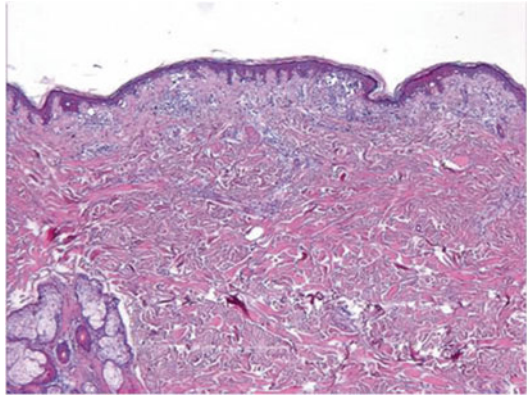

Fig. 46.7 The overlying epidermis may show features of melanoma "in situ"

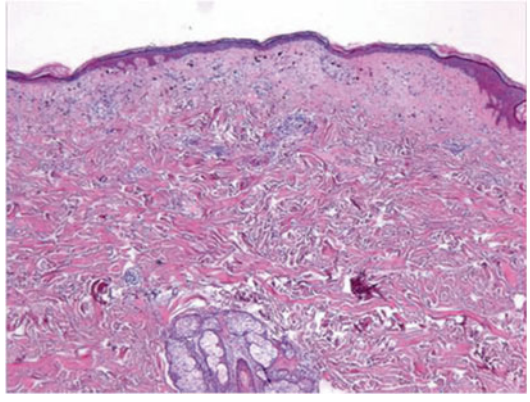

Fig. 46.8 Features of melanoma with underlying regression can also be found

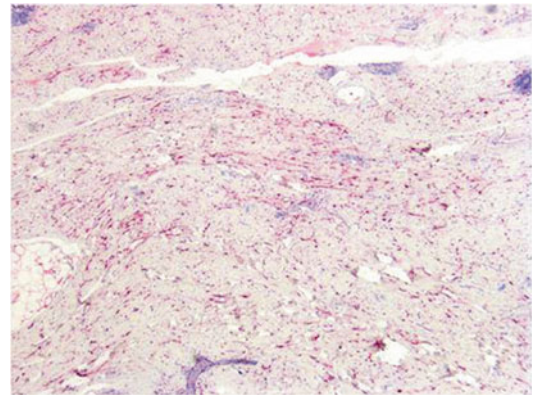

Fig. 46.9 S-100 protein is expressed in almost all cases of DM

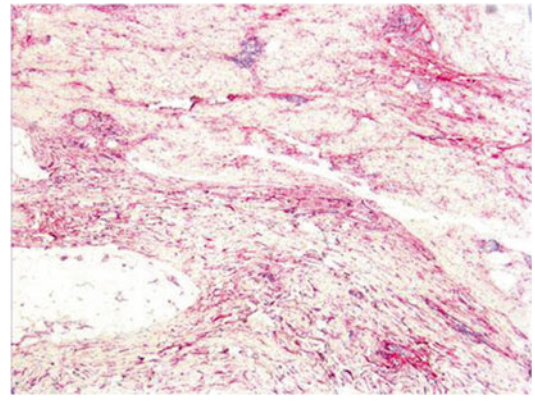

Fig. 46.10 In addition to S-100, p75NGF-R is a useful diagnostic stain in DM

factor receptor) (Figs. 46.9 and 46.10). Melan-A (MART-1) and MITF (microphthalmia transcription factor) are variably positive and with limited value. HMB45 is usually negative. SOX10 is a useful marker, especially in differentiating persistence or recurrence of DM from scar.

Differential Diagnosis

Early lesions of DM may be difficult to differentiate from benign melanocytic lesions embedded within a fibrotic stroma, such as sclerotic blue nevus, desmoplastic Spitz nevus, and desmoplastic

nevus. Apart from architectural and cytologic features, the presence of neurotropism, lymphocytic aggregates, and atypical intraepidermal melanocytic proliferation helps in differentiation of DM from these nevi. DM may also be confused with other benign non-melanocytic lesions such as neurofibroma, cellular neurothekeoma, schwannoma, and dermatofibroma.

The more cellular variants of DM should be distinguished from other malignant spindle-cell neoplasms, such as spindle cell atypical fibroxanthoma, malignant fibrous histiocytoma, dermatofibrosarcoma protuberans, malignant peripheral nerve sheath tumor, spindle cell squamous cell carcinoma, and leiomyosarcoma. A careful clinicopathologic correlation coupled with a complete immunohistochemical analysis aids in establishing the correct diagnosis.

Distinguishing DM, especially recurrent lesions of it, from scar tissue may be very difficult. Accurate evaluation of the arrangement and cytologic features of the proliferating spindle cells is essential. Immunoreactivity for S-100 and SOX10 is very helpful in these situations.

Prognosis

Patients with pDM have a lower frequency of lymph node involvement, a lower locoregional recurrence rate, and a better prognosis than those with conventional melanoma. Head and neck location, male gender, and advanced age are negative prognostic factors. The presence of neurotropism is associated with higher local recurrence rates (Figs. 46.11 and 46.12). Systemic metastases appear to be associated with previous recurrences and tumor thickness. The lung is the predilection site for metastases.

Treatment

The predisposition for local recurrence and neurotropism support the current recommendation of at least 2 cm surgical excision margins for DM. As regional LN involvement in DM occurs less frequently than in other cutaneous melanomas, SLNB may be unnecessary for these patients. However, it should be considered in patients with tumors that show deep infiltration, neurotropism, ulceration, and high mitotic rate. Patients with locally recurrent DM, residual gross tumor, perineural involvement, and narrow/positive excision margins may benefit from adjuvant radiotherapy. In metastatic disease, the efficacy of systemic treatments such as ipilimumab or vemurafenib has to be determined.

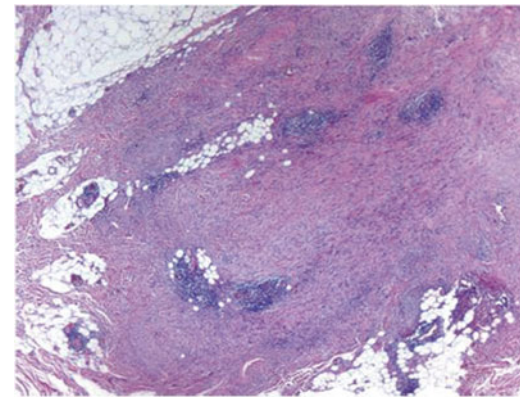

Fig. 46.11 Desmoplastic melanoma. A recurrent lesion is deeply located in the subcutaneous fat below the scar. As the primary lesion, it is also typified by a spindle cell proliferation arranged in fascicles and accompanied by fibrosis and collections of lymphocytes

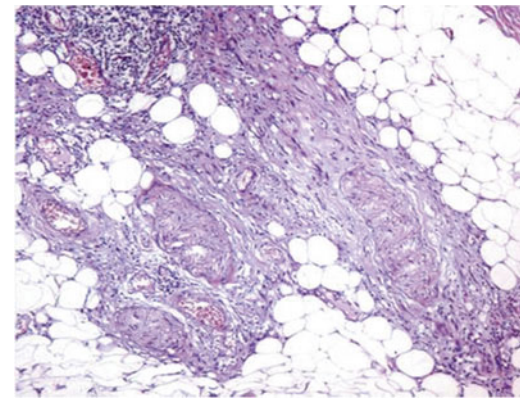

Fig. 46.12 The presence of neurotropism is associated with higher local recurrence rates and dictates the behavior of desmoplastic melanoma

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Signet-Ring Cell Melanoma

47

Sara C. Shalin and Bruce R. Smoller

Introduction

Melanoma with signet-ring cells is a rare histological variant of melanoma first described in 1988. The challenge of this diagnosis lies in its mimicry with the more commonly seen adenocarcinoma with signet-ring cells, as there has been a suggestion that melanoma with signet-ring cells may be more often observed in metastatic or recurrent lesions. Interestingly, though unusual in human melanoma (estimated to occur in approximately 0.5 % of tumors), this morphological variant has been reported more frequently in animals.

Clinical Presentation

Initial reports seemed to suggest that tumors with this morphology were more likely to be amelanotic and metastatic. Indeed, a large proportion of the case reports within the literature document this morphological variation occurring in metastatic and recurrent melanoma, sometimes in the absence of a primary diagnosis. However, subsequent reports have shown that the signet-ring pattern can be seen in both pigmented and primary melanocytic lesions. Primary melanoma with signet-ring cells has been reported presenting as plaque-like lesions as well as tumor nodules. A single case of a primary melanoma occurring at the gastroesophageal junction has been reported.

Pathology

Signet-ring cells are characterized by intracytoplasmic vacuolization. The nucleus is pushed to the side of the cell, and a single large intracytoplasmic vacuole indents or flattens one side of the nucleus, mimicking a signet ring (Fig. 47.1). Cell size may range from small to giant. Ultrastructural studies have demonstrated that the signet-ring cell melanocytes demonstrate clusters of intermediate filaments, likely vimentin, within their cytoplasm. Signet-ring cells may represent a portion of or the exclusive tumor morphology. Diagnosis may be aided by the presence of associated areas of more conventional-appearing melanoma (Fig. 47.2). Signet-ring cells have been described as occurring both within the intraepidermal and dermal components of melanoma.

Immunohistochemical staining may be necessary to diagnose melanoma with signet-ring cells. Typically, the tumors express S-100 protein, although rarely, tumors lacking S100 protein

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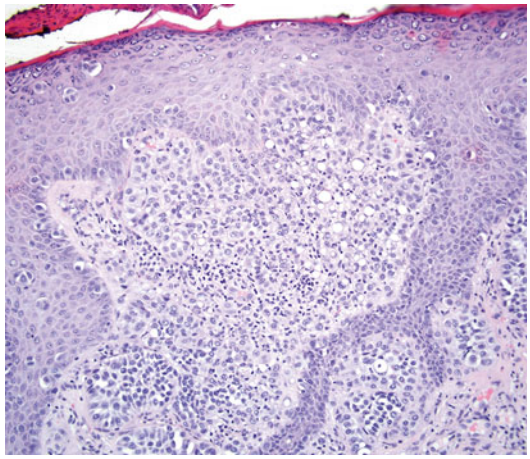

Fig. 47.1 Signet ring cell melanoma. Low-power magnification demonstrates an intraepidermal proliferation of atypical melanocytes with pagetoid spread. Within the dermis, there are sheets of atypical melanocytes, some of which demonstrate signet-ring morphology

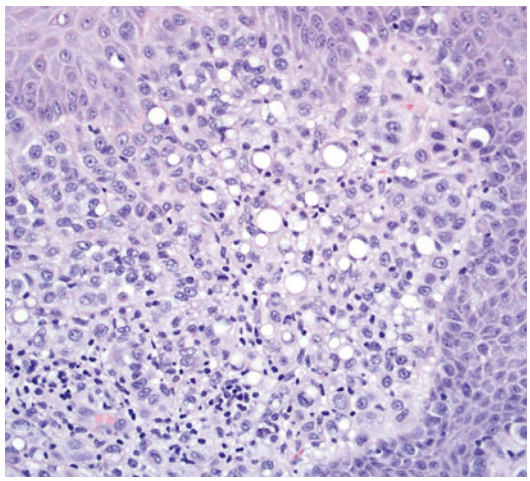

Fig. 47.2 Signet ring cell melanoma. High magnification delineates enlarged pleomorphic cells, some of which have a single intracytoplasmic vacuole. The nucleus is pushed eccentrically and is indented. A dermal mitotic figure is evident. These cells expressed MART-1

expression or only demonstrating focal positivity are reported. Other conventional melanocytic markers such as HMB45 and Mart-1 may be expressed but are less frequently positive.

Differential Diagnosis

Signet-ring cells may be encountered in benign melanocytic nevi as well as melanoma (Fig. 47.3), and as such, the presence of such morphology should not automatically trigger a diagnosis of malignancy. Signet-ring cell melanoma also has overlapping histological features with other histological variants of melanoma, including rhabdoid and balloon cell melanoma. In melanoma with rhabdoid features, the nucleus is pushed to the side, but the cytoplasm acquires a dense pink, eosinophilic rather than clear appearance, thereby mimicking primitive rhabdomyoblasts. In contrast, balloon cell change, like signet-ring change, is characterized by clear cytoplasm within the melanocyte, but the nucleus is central, rather than eccentrically placed, and there may be multiple intracytoplasmic vacuoles. Balloon cell change is thought to represent degeneration and overproduction of melanosomes, and electron microscopy does not demonstrate accumulation of vimentin filaments.

Signet-ring cells are classically described in mucin-secreting adenocarcinomas, and melanoma with a predominant signet-ring cell pattern can closely mimic such a tumor. The presence of intracytoplasmic mucin or expression of cytokeratin would support a diagnosis of signet-ring adenocarcinoma, whereas the absence of mucin or cytokeratin expression or the presence of associated pigment would favor a melanoma. Immature adipocytes (lipoblasts) may sometimes mimic signet-ring cells and can be distinguished by lipid material within the cytoplasm and nuclear vacuolization. Signet-ring cells have also been described in vascular tumors such as hemangioendothelioma, some epithelioid smooth muscle tumors, and lymphomas. In such cases, immunohistochemical stains may be necessary to determine the tumor cell derivation. Other primary cutaneous neoplasms, including squamous cell carcinoma, basal cell carcinoma, and adnexal tumors, can sometimes exhibit signet-ring cells.

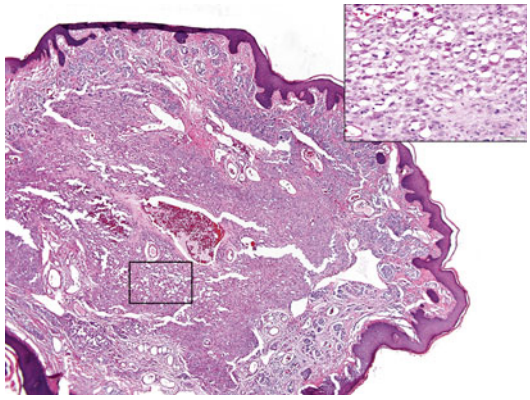

Fig. 47.3 Signet-ring cell change in a dermal nevus. Scanning magnification shows a predominantly intradermal nevus. Focally (inset), signet-ring cells are present

Prognosis

Given the propensity for this histological variant to be seen in metastatic lesions, some authors have considered it to represent a poor prognostic sign; however, the rarity of this morphology makes it difficult to study systematically in primary melanomas. Most likely, the prognosis of melanomas demonstrating signet-ring cell change will depend on the tumor depth (Breslow measurement).

Treatment

As for conventional melanoma, melanoma with signet-ring cells should be excised with appropriate surgical margins. Sentinel lymph node sampling should be considered based on the primary tumor (Breslow) depth and other prognostic indicators within the biopsy report. Chemotherapy, immune-modulating therapy, and targeted drug therapy are used in cases of metastatic disease.

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Myxoid Melanoma

48

Elisa Cinotti and Franco Rongioletti

Introduction

Malignant myxoid melanoma (MMM) is a rarely reported subtype of malignant melanoma, characterized by a myxoid stroma. This particular stroma results from enhanced production of glycosaminoglycans, primarily in the form of hyaluronic acid of mesenchymal origin, as demonstrated by the sensitivity of the mucin to hyaluronidase, and its lack of staining with periodic acid–Schiff (PAS) and mucicarmine.

Clinical Features

In 1986, Bhuta et al. first described metastatic malignant melanoma that exhibited prominent myxoid change in the stroma. Subsequently, less than 50 cases of MMM, including primary lesions and metastases, have been reported. Myxoid metastases are more frequent than primary myxoid melanoma. MMM affects an old population. Men tend to be affected slightly more often than women. Clinically, MMM appears as conventional melanoma. Lesions tend to occur, in decreasing order, on the extremities, trunk/back, and head/neck. Extracutaneous sites including the sinonasal passages have been reported.

Pathology

Melanocytes are embedded in a myxoid stroma, composed of basophilic, acidic mucin, that may be either focal or diffuse (Fig. 48.1). They are arranged in nests or cords and are spindle, round, or stellate shaped (Fig. 48.2) with atypical cytologic features. They have prominent nucleoli. Mitotic figures may or may not be present, and there may be a sparse inflammatory infiltrate in the surrounding dermis, sometimes with mast cells and/or multinucleated giant cells. Tumors are mostly amelanotic.

Distinction of primary from secondary metastatic MMM is based on the demonstration in the primary lesions of an atypical intraepidermal melanocytic proliferation (Fig. 48.3). Myxoid metastasis of melanoma is usually associated with a primary neoplasm that does not manifest a myxoid morphology.

Immunohistochemistry analysis of the tumor shows uniform staining of S-100, while staining with HMB 45 or melan-A can be negative. Colloidal iron or Alcian blue at low pH detects mucin in the stroma.

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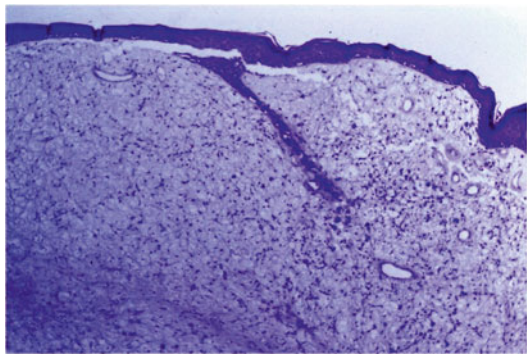

Fig. 48.1 Myxoid melanoma. Melanocytes are embedded in a myxoid stroma, composed of basophilic, acidic mucin, that may be either focal or diffuse

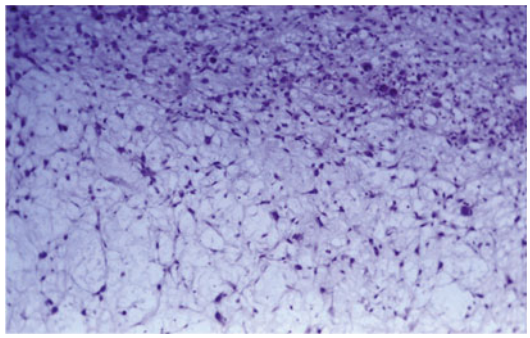

Fig. 48.2 Myxoid melanoma. Spindle, round, stellate-shaped, and atypical melanocytes embedded in a myxoid stroma

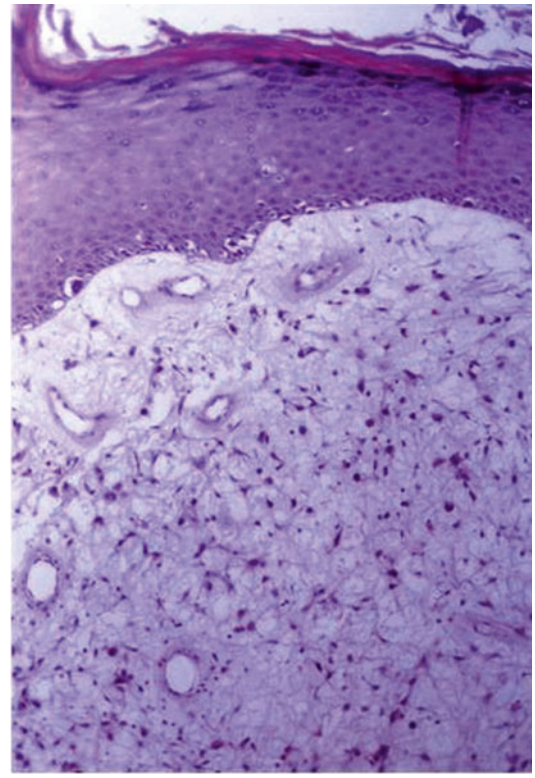

Fig. 48.3 The pattern of intraepidermal melanocyte involvement can be subtle, with only focal irregular proliferation in the lower layer overlying a myxoid proliferation

Differential Diagnosis

Histologically, MMM should be differentiated from other epithelial mucin-containing tumors such as metastatic adenocarcinomas, and malignant sweat duct tumors, and from (mesenchymal) mucin-containing soft tissue tumors such as low-grade fibromyxoid sarcoma, low-grade myofibroblastic sarcoma, myxoid dermatofibrosarcoma protuberans, myxoid liposarcoma, extraskeletal myxoid chondrosarcoma, metastatic chordoma, myxoid rhabdomyosarcoma, myxoid synovial sarcoma, myxoid follicular dendritic cell sarcoma, nerve sheath myxoma, neurothekeoma, and malignant melanotic schwannoma. The malignant neoplasms of the sweat gland and duct manifest keratin positivity in most cases, as do metastatic carcinomas such as those of the breast and lung. Furthermore, these tumors usually express epithelial mucin and not mucin of mesenchymal origin. Low-grade fibromyxoid sarcoma and low-grade myofibroblastic sarcoma are generally S-100 negative. Myxoid dermatofibrosarcoma protuberans is CD34 negative, unlike its conventional counterpart, but can be distinguish by the lack of S-100 protein expression. Moreover, it stains positively for SMA. Liposarcoma rarely presents as a primary skin neoplasm and usually has plexiform, delicate "chicken-wire" vasculature that is lacking in MMM. Moreover, liposarcomas manifest weak cytoplasmic membrane rim staining with S-100 protein quite unlike that seen in a melanocytic neoplasm. Extraskeletal myxoid chondrosarcoma is a malignant mesenchymal neoplasm of uncertain differentiation (despite its name, there is no evidence of cartilaginous differentiation). It has a multinodular architecture defined by fibrous

septa that divide the tumor into hypocellular lobules with myxoid matrix. It is weakly positive for S-100 in only a minority of cases, and it is characterized by *NR4A3* (9q22) gene rearrangement. In chordoma, a malignant tumor showing notochordal differentiation, the cells are separated into lobules by fibrous septa and manifest spongelike or bubbly cytoplasmic vacuolation (physaliphorous cells). The expression of S-100 protein and cytokeratins enables distinction from MMM. Rhabdomyosarcoma characteristically is desmin positive and S-100 negative, unlikely melanoma. Synovial sarcoma rarely presents as a primary skin neoplasm. Around half of such tumors express S-100 protein, whereas most display epithelial differentiation (epithelial membrane antigen and/or cytokeratins expression), and most have the translocation t(X;18)(p11;q11) that leads to the formation of the *SS18-SSX* fusion gene. The follicular dendritic cell sarcoma expresses S-100 protein and epithelial membrane antigen, as well as CD21 (Epstein-Barr virus receptor on B lymphocytes), CD23 (receptor FcεRII for IgE), and CD35 (a monocyte marker). Neural tumors are particularly difficult to differentiate from MMM. However, tumors of neural crest origin, such as neurothekeomas and schwannomas, are S-100 positive but usually HMB45 negative.

Desmoplastic melanomas, common acquired nevi, and cellular blue nevi can also present a myxoid stroma. Nonneoplastic conditions that should be considered in the differential diagnosis are papular mucinosis and nodular fasciitis.

Prognosis

The prognosis appears to be equivalent to other primary melanomas.

Treatment

The treatment is the same of conventional melanoma.

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Rhabdoid Melanoma

49

Jerad M. Gardner and Bruce R. Smoller

Introduction

A variety of skin and soft tissue tumors may display "rhabdoid" cytologic features defined most simply as the presence of a large eosinophilic hyaline globule causing peripheral displacement of the nucleus in some or all of the tumor cells. Melanoma may rarely display rhabdoid features, most often in metastatic lesions. Only a handful of cases of primary rhabdoid melanoma have been reported in the literature. Recognition of this entity is important to avoid confusion with other rhabdoid neoplasms.

Clinical Features

It has no apparent age or sex predilection and has been reported in both males and females ranging from the first to eighth decades. Primary rhabdoid melanomas have been reported in the scalp, back, shoulder, and thigh. Metastatic rhabdoid melanomas are most commonly identified in the lymph nodes but may also present in the lung, liver, soft tissue, small bowel, and skin. Several of the reported cases of apparently metastatic rhabdoid melanoma had no identifiable primary tumor despite extensive clinical workup. The clinical workup should exclude the possibility of a primary melanoma arising in a non-cutaneous site such as mucosa.

Pathology

Primary rhabdoid melanoma may have histological features typical of primary conventional melanoma with the additional finding that some of the cells display rhabdoid features. The tumor is typically composed of sheets of polygonal cells with round nuclei, vesicular chromatin, and abundant eosinophilic cytoplasm (Fig. 49.1). Perinuclear eosinophilic hyaline globules which peripherally displace the nucleus (rhabdoid features) may be seen in only a subset of tumor cells or the tumor may be composed almost entirely of rhabdoid melanocytes (Figs. 49.2, 49.3 and 49.4). Most often, the cells lack melanin pigment although focal pigmented cells may be seen in some cases. Alternatively, two of the reported cases of primary rhabdoid melanoma displayed a dermal nodule of rhabdoid melanocytes arising in the background of a benign

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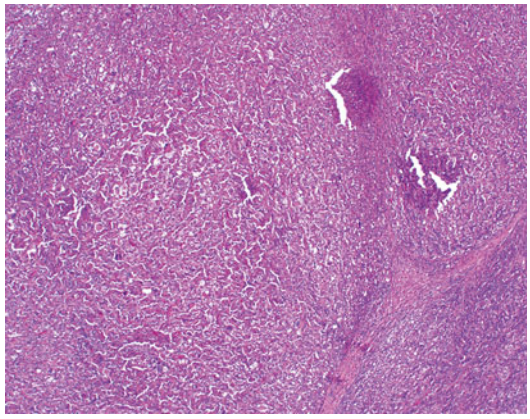

Fig. 49.1 Sheets of atypical melanocytes with abundant eosinophilic cytoplasm comprise rhabdoid melanoma

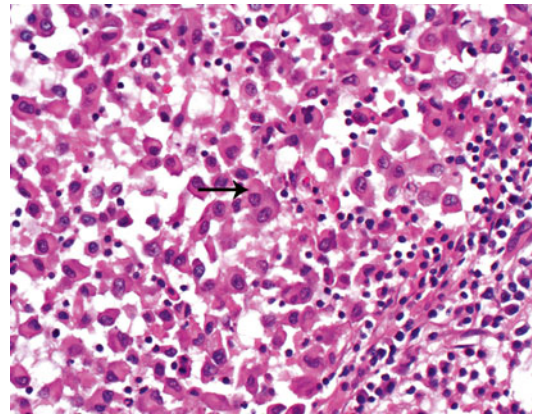

Fig. 49.4 The presence of perinuclear eosinophilic hyaline globules (*arrow*) which peripherally displace the nucleus is a characteristic feature

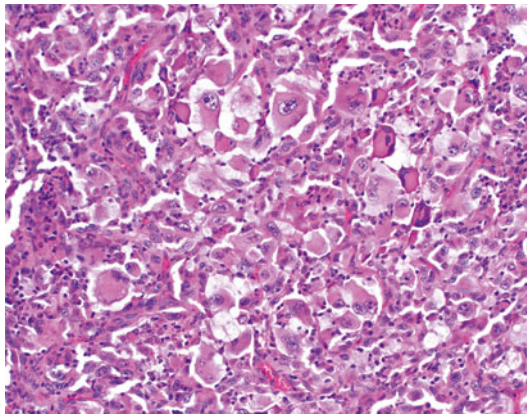

Fig. 49.2 The tumor cells have marked nuclear atypia and abundant densely eosinophilic cytoplasm. The appearance is somewhat reminiscent of rhabdomyoblasts

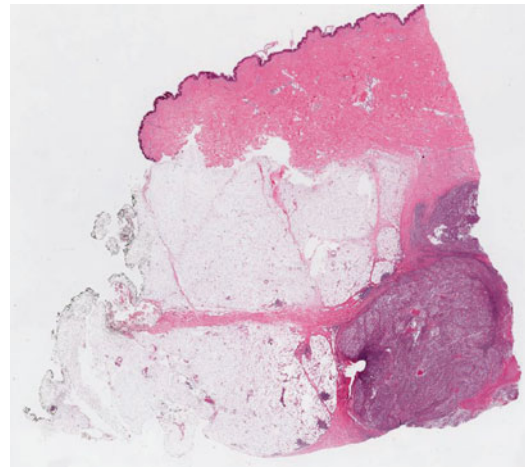

Fig. 49.5 Metastatic rhabdoid melanoma displays a nodular proliferation of melanocytes in the subcutis similar to cutaneous metastases of conventional melanoma

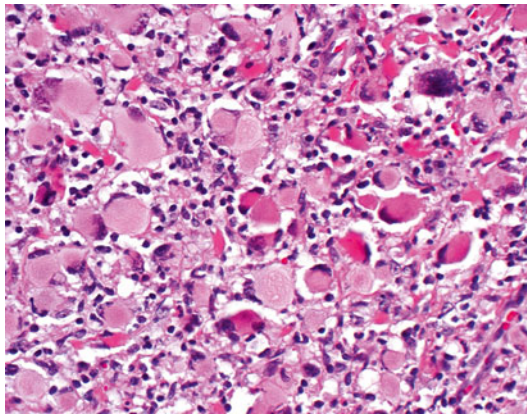

Fig. 49.3 The tumor cells have marked nuclear atypia and abundant densely eosinophilic cytoplasm. The appearance is somewhat reminiscent of rhabdomyoblasts

melanocytic nevus. Metastatic rhabdoid melanoma displays a nodular proliferation of melanocytes within the dermis, subcutis, or other tissues to which the tumor has metastasized (Fig. 49.5). The immunophenotype of rhabdoid melanoma is highly variable. Expression of S-100 protein and HMB45 is seen in many cases, although a subset of cases may lose expression of either S-100 protein and/or HMB45 and may gain expression of pancytokeratin, desmin, and/or neuroendocrine markers. In cases that do not express melanocytic

markers, the diagnosis can only be made in the context of clinical history, and extreme caution must be used to avoid missing cutaneous myoepithelial carcinoma, cutaneous rhabdomyosarcoma, or other neoplasms which could have similar immunophenotypes. Ultrastructurally, the hyaline perinuclear globules of rhabdoid melanoma are most commonly composed of whorled filamentous bodies with entrapped lipid and organelles, although in some cases, they are composed of intermediate filaments arranged either into elongated curved bundles or condensed, twisted sheaves similar to squamous cell tonofilaments.

Differential Diagnosis

The histological differential diagnosis is broad and includes other skin and soft tissue neoplasms that may have rhabdoid cytologic features, including malignant extrarenal rhabdoid tumor, proximal-type epithelioid sarcoma, primary cutaneous or metastatic rhabdomyosarcoma, myoepithelioma/mixed tumor, myoepithelial carcinoma, and poorly differentiated carcinoma.

Prognosis

Rhabdoid melanoma appears to have a biological behavior and prognosis similar to that of conventional melanoma.

Treatment

Rhabdoid melanoma should be treated according to conventional melanoma protocols.

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Balloon Cell Melanoma

50

Elisa Cinotti and Franco Rongioletti

Introduction

Balloon cell malignant melanoma (BCMM) is a rare histological variant of malignant melanoma first reported by Gardner in 1970.

Clinical Features

The clinical presentations are variable: BCMM have been characterized as nodular, ulcerated, pedunculated, polypoid, and papillomatous.

Pathology

BCMM is composed predominantly of large foamy cells with abundant, vacuolated cytoplasm (balloon cells) that should compose at least 50 % of the tumor cells (Fig. 50.1). Beyond this observation, it shares the cytologic features of the other subcategories of malignant melanoma, such as pagetoid spreading, discohesion, nuclear pleomorphism, intranuclear cytoplasmic pseudoinclusions, atypia, and mitoses (Fig. 50.2).

The cells mainly show the immunohistochemical features of conventional melanoma cells (S-100, HMB45, melan-A expression) (Fig. 50.3). Although it is generally believed that balloon melanoma cells represent a degenerative change, the immunohistochemical and electron microscopic findings suggest that the balloon tumor cells are most likely metabolically active melanocytic cells. In particular, electron microscopy shows abundant cytoplasmic membrane-bound vacuoles, few or no melanosomes, and only infrequent abnormal premelanosomes.

Balloon cells are usually sparse in the primary melanoma but have a potential of constituting the entire lesion in metastasis. In few cases, the metastasis of melanoma is composed of balloon cells, whereas the primary melanoma does not exhibit any balloon cells and predominantly consists of spindle-shaped and epithelioid cells.

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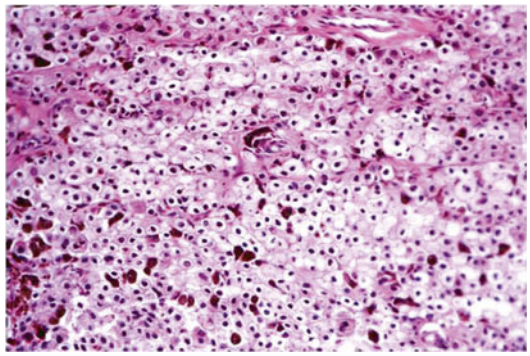

Fig. 50.1 Balloon cell melanoma. Enlarged polygonal cells with vacuolated (*clear*) cytoplasm and central hyperchromatic nucleus in at least 50 % of cells

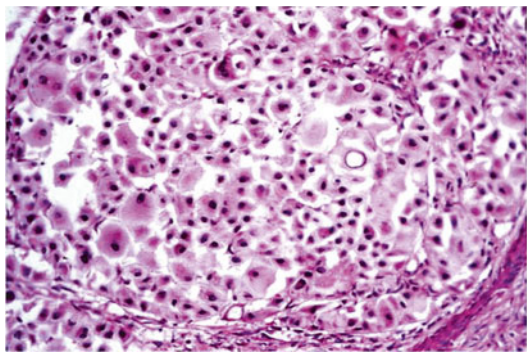

Fig. 50.2 Balloon cell melanoma. Nuclear pleomorphism, intranuclear cytoplasmic pseudoinclusions, atypia, and mitoses help to distinguish melanoma from balloon cell nevus

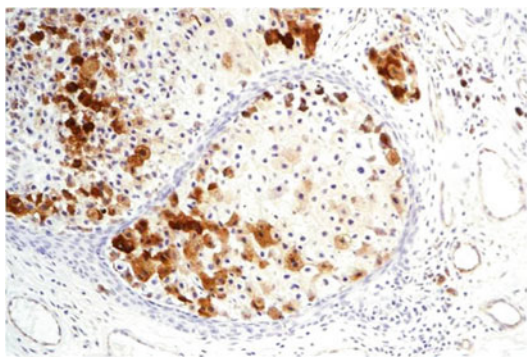

Fig. 50.3 Balloon cell melanoma. HMB45 positivity helps to rule out other clear cell tumors

A peculiarity of BCMM is the general lack of melanin, in contrast to conventional melanoma and balloon nevus cells.

Differential Diagnosis

Clinically, BCMM could mimic other types of malignant melanoma, basal cell carcinoma, squamous cell carcinoma, fibromatous lesions, and cutaneous adnexal tumors.

Histological differential diagnosis are clear cell tumors such as clear cell sarcoma (malignant melanoma of soft tissue), clear cell carcinoma (including basal cell carcinoma, adnexal tumors such as malignant clear cell acrospiroma and clear cell syringoma, and metastases from tumors of the kidney, breast, large bowel, lung, salivary glands and thyroid), malignant granular (clear) cell tumor, hibernoma, xanthoma, sebaceous neoplasms, seminoma, perivascular epithelioid cell tumors (PECOMAS), and atypical fibroxanthoma.

As with melanoma, clear cell sarcoma stains positively for S-100, HMB45, melan-A, and PAS. However, clear cell sarcoma is composed of packed nests of fusiform cells, the nuclei lack pleomorphism, and molecular analysis shows the fusion gene *EWS/ATF*. PECOMA stains positively for HMB45, melan-A, and in 30 % of cases for S-100 but can be differentiated by the expression of smooth muscle actin. Granular cell tumors have granular PAS-positive cytoplasm but may be distinguished from melanoma by negative melanoma markers. Xanthomatous lesions can also be differentiated by the lack of melanoma markers. Sebaceous lesions have "bubbly" cytoplasm and the nuclei show a scalloped border. They are distinctly S-100 and HMB45 negative and stain positively for epithelial membrane antigen. Renal clear cell carcinoma often shows prominent vascular stroma, hemorrhage, and tumor necrosis. It can be differentiated with positive staining for cytokeratin and CD10. Melanoma with clear cell changes has been considered different from BCMM only from a semantic

point of view; in fact, distinctive criteria in the former are the absence of cytoplasmic xanthomatization as well as the position of nucleus that is centrally located in balloon cells and eccentric in clear cells. However, a unifying concept that they represent morphological expressions of the same alteration in melanogenesis has been suggested.

Balloon cells have been reported in nevi, including intradermal, halo, and combined nevi[3]. However, balloon cell nevus has centrally located nuclei with no nuclear pleomorphism and no mitotic activity. Cell maturation is an important clue to benignity, and though rare, tumor necrosis, when seen, is supportive of melanoma. Multinucleated giant balloon cells can be found in both nevi and melanoma.

Prognosis

Prognosis usually correlates with the tumor thickness similar to other histological types of cutaneous melanoma. In a study of Kao et al., 19 (57.5 %) of 33 patients died of disseminated tumors from 2 months to 12 years after the initial treatment.

Treatment

Early wide surgical excision of the tumor is the treatment of choice. The treatment is the same as conventional melanoma.

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Minimal Deviation Melanoma/ Nevoid Melanoma

51

Irina Margaritescu and A. Doru Chirita

Introduction

"Borderline melanoma" (BM), "minimal deviation melanoma" (MDM), and nevoid melanoma (NM) represent variants of melanoma that may simulate a benign melanocytic lesion, both clinically and histopathologically. When the melanocytes are confined to the papillary dermis only, the applied term is "borderline melanoma." However, the concept of "borderline melanoma" and "minimal deviation melanoma" has been a source of considerable controversy and has not gained universal acceptance. This is due in principle to the absence of standardized criteria. Moreover, these nominations seem to represent a basket weave for all the difficult melanocytic lesions.

Clinical Features

NM may equally affect men and women from all age groups (range 16–95), with a mean age at presentation of 45 years. The back is the preferred affected site in men and the extremities in women, but it may also appear in the head and neck region. Usually, it presents as a well-circumscribed, slowly growing nodule, 1–2 cm in diameter, characterized by a skin-colored, grayish, dark brown, or black appearance and a dome-shaped or verrucous surface (Fig. 51.1). It may mimic a benign lesion such as a melanocytic nevus, seborrheic keratosis, fibroepithelial polyp, or a cyst.

Pathology

"MDM" presents as an expansile nodule composed of relatively uniform, moderately atypical melanocytes. The cells may have an epithelioid or spindle cell appearance and exhibit only moderately enlarged nuclei with irregular chromatin distribution and an increased nuclear–cytoplasmic ratio. Mitotic figures are usually identified, but the mitotic index is quite low. There is no maturation of the cells or nests with progressive descent in the dermis.

NM presents as a raised, dome-shaped, polypoid or papillomatous melanocytic proliferation, with or without a verrucous surface, mimicking a dermal nevus (Fig. 51.2). There is an apparent maturation in respect to the size of melanocytes and nests, with progressing descent in the dermis (Fig. 51.3). Frequently, the deep margin has an infiltrative growth pattern. The neoplasm is

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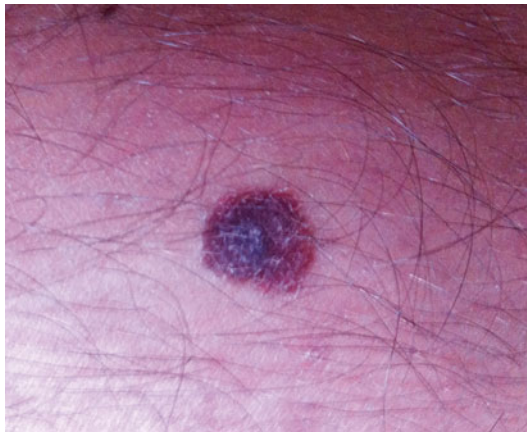

Fig. 51.1 Well-circumscribed, slowly growing lesion, 2 cm in diameter, with *dark brown* appearance, mimicking a melanocytic nevus

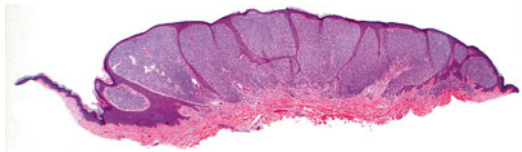

Fig. 51.2 At scanning magnification, the lesion is large, polypoid, relatively symmetrical, and well circumscribed, reminiscent of a congenital melanocytic nevus. However, the high cellular density is the first clue that points to the real nature of the lesion

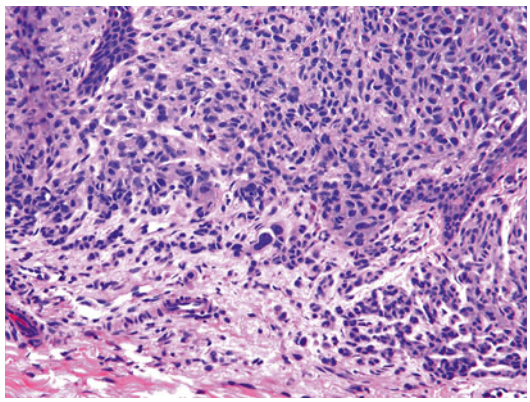

Fig. 51.3 Careful scrutiny of the lesion shows no real maturation and no stromal reaction

composed of a mildly pleomorphic population of melanocytes with hyperchromatic nuclei and prominent nucleoli (Fig. 51.4). There is an increased mitotic activity in the deeper aspects of the lesion. The intraepidermal melanocytes are arranged as both single cells and nests at the dermal–epidermal junction. Pagetoid spread of melanocytes may be present in a proportion of cases. Perineural infiltration may be occasionally encountered. Also, a peritumoral lymphocytic infiltrate is usually present.

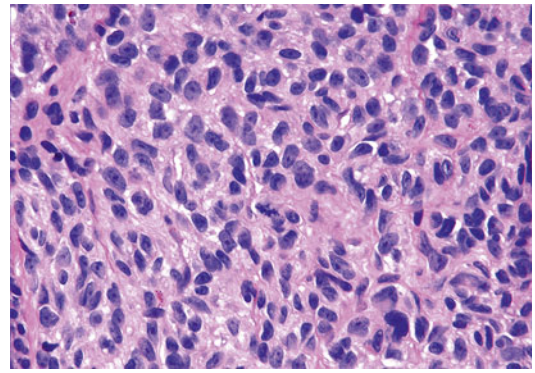

Fig. 51.4 Melanocytes are mildly pleomorphic with hyperchromatic nuclei and prominent nucleoli. Atypical mitotic figures are usually seen in the deeper aspects of the lesion

Immunohistochemistry: HMB45 stains melanocytes in a patchy or diffuse pattern within the dermis in nevoid melanoma in contrast with a stratified pattern seen in benign nevi. MIB-1 and cyclin D1 may be of help in demonstrating an increased proliferative activity.

Differential Diagnosis

The differential diagnosis of NM includes various types of melanocytic nevi with atypical features (congenital and congenital pattern nevi, halo nevi, traumatized and inflamed nevi, blue nevus, cellular blue nevus, combined nevus, spindle and epithelioid cell nevus, nevi in pregnancy, and nevi from particular anatomic sites) and metastatic melanoma.

The most important histological features that allow discrimination of NM from all these benign melanocytic nevi are the lack of maturation, subtle pleomorphism, and the presence of mitotic activity especially in the lower third of the lesion. In very difficult cases, a careful clinicopathologic

correlation (age, anatomic site, pregnancy, presence of trauma, etc.) coupled with appropriate immunohistochemical studies is essential in establishing the correct diagnosis.

Prognosis

The prognosis of NM is similar to that of conventional invasive melanoma in the same stage group. The most important prognostic factors are the clinical stage and Breslow thickness.

Treatment

The management of patients with NM should be the same as for those with conventional melanomas in the same stage disease. Complete excision of the tumor with wide surgical margins and sentinel lymph node biopsy in selected cases represents the treatment of choice for early stage melanoma. For advanced disease, immunotherapy with interferon or interleukin-2 and adjuvant chemotherapy with single-agent dacarbazine or combination chemotherapy may be of benefit. Targeted therapy with imatinib for those patients with mutations or amplification of the Kit proto-oncogene has proved to be an effective treatment option. Recently, BRAF inhibitors (vemurafenib and dabrafenib), and a MEK inhibitor (trametinib), were approved by the FDA for advanced stage melanoma with BRAF V600E or V600K mutations. Ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, has demonstrated remarkable promise in patients with metastatic melanoma.

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Spitzoid Melanoma

52

Franco Rongioletti

Introduction

Spitzoid melanoma is a controversial melanocytic malignant neoplasm. Although the 2009 Workshop of the International Melanoma Pathology Study Group has discouraged the usage of this term until this subset of melanomas can be more rigorously defined by phenotypic and genetic studies, spitzoid melanoma is still used to describe melanomas with architectural and/or cytologic features resembling Spitz nevus. Spitzoid melanoma indeed seems not to have its own distinguishing features but is defined in comparison with Spitz nevus, especially from a histological point of view.

Clinical Features

Spitzoid melanoma is considered a melanoma subtype often developing in children, while it seems to be more common in adults. The neoplasm is characterized by a changing nodule that can be amelanotic, pigmented, or variegated in color (Fig. 52.1), crusted, and ulcerated, often reaching 10 mm or more in diameter. The head and extremities are the most frequent involved sites in the childhood type. Female predominance occurs in spitzoid melanoma.

Pathology

Spitzoid melanoma shares many histopathologic features with Spitz nevus, and it is one of the most difficult and problematic diagnoses in dermatopathology. The mainstay for the diagnosis is nests of variable size and shape with large spindle or epithelioid cells characterized by abundant eosinophilic cytoplasm and prominent eosinophilic nucleoli. Although there are no specific histopathologic diagnostic criteria for spitzoid melanomas, these malignancies are usually asymmetrical, lack both circumscription and maturation, and exhibit high cell density, deep mitoses, an expansive growth pattern and consumption of the epidermis or ulceration (Figs. 52.2–52.6).

Compared to Spitz nevus, the melanocytic epidermal component is usually not well demarcated with spreading of melanocytes at the edges. The junctional nests are irregularly shaped and unevenly distributed with irregular pseudoacantholytic clefts, and in some areas, single melanocytes predominate showing a pagetoid spreading (Fig. 52.3). The dermal component is characterized by an asymmetrical nodular proliferation of irregular and crowded nests with enlarged, atypical epithelioid or spindle-shaped melanocytes that are often amelanotic and lack maturation (Figs. 52.4 and 52.5).

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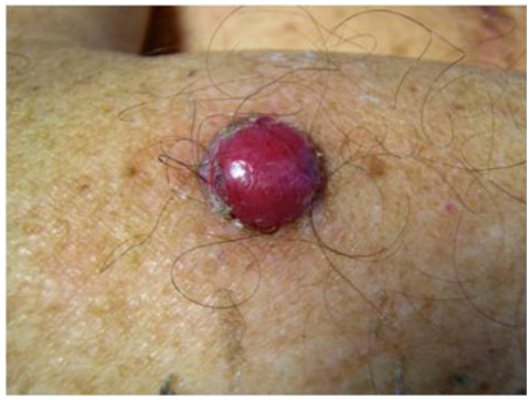

Fig. 52.1 Spitzoid melanoma. An erythematous fast-growing nodule on the upper arm of a 49-year-old man

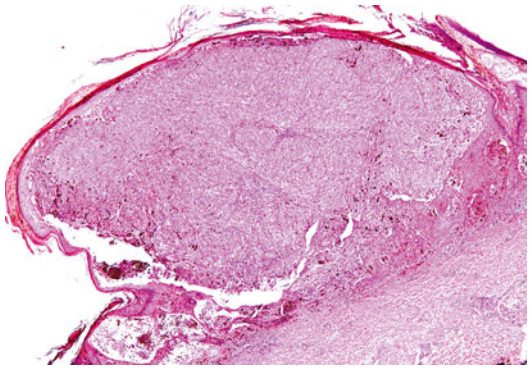

Fig. 52.2 Spitzoid melanoma. An asymmetrical, expansive nodule showing high cell density and consumption of the epidermis

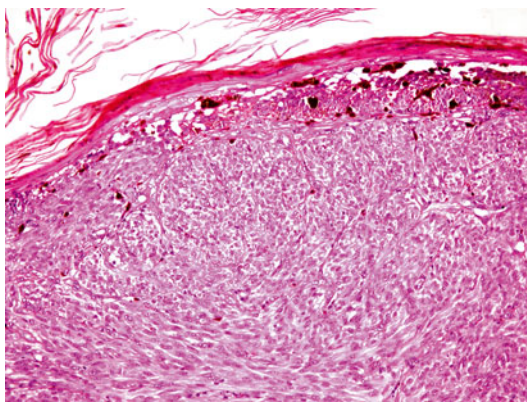

Fig. 52.3 Spitzoid melanoma. A spindle-shaped and epithelioid eosinophilic proliferation. The junctional nests are irregularly shaped and unevenly distributed with irregular pseudoacantholytic clefts

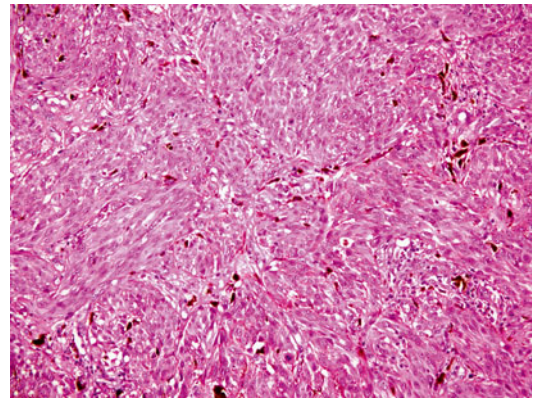

Fig. 52.4 Spitzoid melanoma. The dermal component is characterized by a nodular proliferation of irregular and crowded nests with enlarged, atypical epithelioid, or spindle-shaped melanocytes lacking maturation

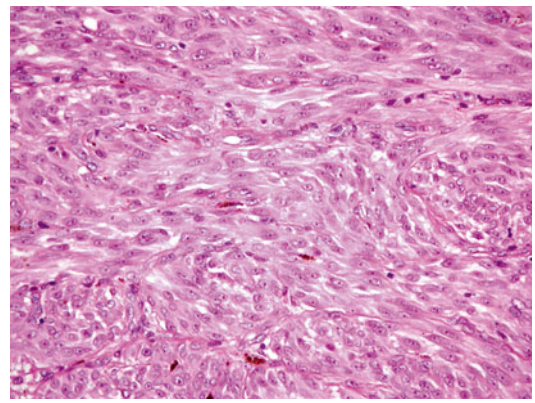

Fig. 52.5 Spitzoid melanoma. Atypical epithelioid or spindle-shaped melanocytes with abundant eosinophilic cytoplasm and prominent eosinophilic nucleoli. Deep mitoses are present in the deep dermal component

The phenomenon of zonation (similar appearance of melanocytes along horizontal levels of the lesion) is usually absent. Spitzoid melanoma has a higher degree of cytologic atypia with more pleomorphic, hyperchromatic nuclei that contain large or multiple nucleoli (Figs. 52.7 and 52.8). The deep dermal component shows an expansile growth that involves the superficial subcutaneous tissue rather than an infiltrative pattern. Melanocytes in mitosis are an important clue; more than three dermal mitoses per high-power field, mitoses in the deeper parts of the lesion, and atypical mitoses favor a diagnosis of spitzoid melanoma. The epidermis may

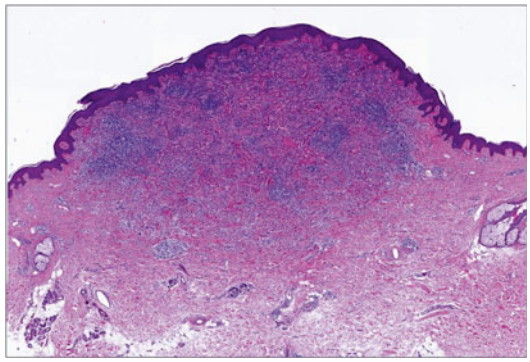

Fig. 52.6 Spitzoid melanoma. Another asymmetrical dermal-based tumor (Courtesy of H.Kutzner, Friedrichshafen)

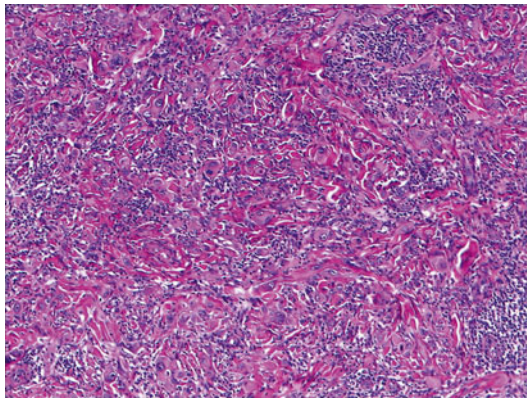

Fig. 52.7 Spitzoid melanoma. This spitzoid melanoma has a higher degree of cytologic atypia with lack of maturation and a dense "brisk" lymphoplasmacytic infiltrate

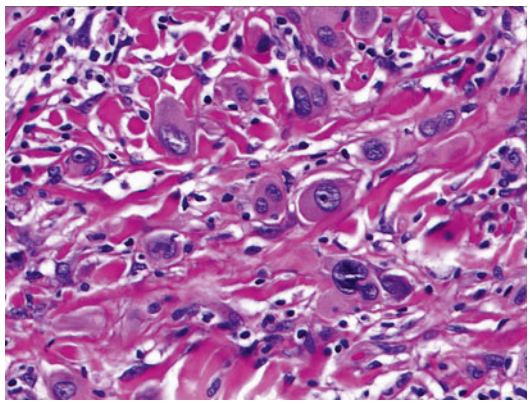

Fig. 52.8 Spitzoid melanoma. Spitzoid melanocytes have a higher degree of cytologic atypia with more pleomorphic, hyperchromatic nuclei that contain large or multiple nucleoli

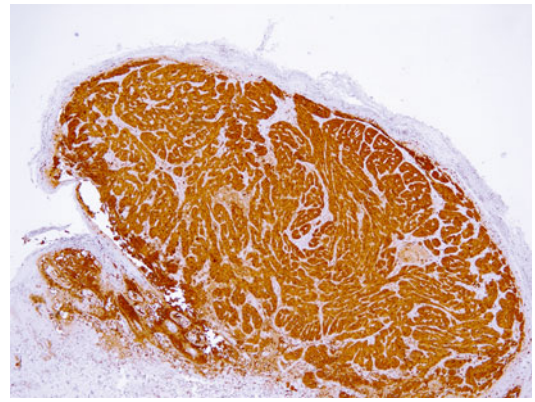

Fig. 52.9 Spitzoid melanocytes are positive for HMB45

ulcerate or is atrophic showing epidermal consumption. Kamino bodies are not features of spitzoid melanoma, and when they are present in a spitzoid neoplasm, a diagnosis of nevus is favored. A dense inflammatory lymphoplasmacytic infiltrate, lack of adnexal structures, areas of necrosis, solar elastosis, regression with or without melanosis, vascular invasion, and neural infiltration all are features that favor melanoma. Recently, five subtypes of spitzoid melanoma have been suggested, i.e., "genuine" similar to small compound Spitz nevus, "uniform" including intradermal spitzoid neoplasm composed of a sheet of epithelioid cells with radical absence of adnexal appendages and little or any collagen, "packed" including intradermal spitzoid neoplasm with very compact nests and dermal artifactual breakages, "polypoid," and "pigmented" including compound spitzoid neoplasm with striking amounts of melanin both in superficial and deep dermis with irregular distribution and melanophages.

While no specific immunohistochemical marker or molecular and genetic test still exists to distinguish Spitz or spitzoid benign neoplasm from spitzoid melanoma, a combination of immunohistochemical stains has been proposed as a useful tool. This panel includes HMB45, (Fig. 52.9), Ki-67/MIB-1, CD99, p16, Neuropilin-2, Bcl-2, cyclin D1, p53, and p21 among others (Figs. 52.6, 52.7, 52.8 and 52.9). HMB45 is evaluated according to a maturation gradient. If the immunostain is expressed

throughout all of the lesion or in a patchy distribution to include deep melanocytic nests, this is considered a sign of malignancy. If there is positive staining at the top of the lesion with loss of staining in the deeper part into the dermis, this favors Spitz nevus. Ki-67/MIB-1 is suggested to be a useful marker in thick and noninflammatory neoplasms and a nuclear proliferation index of 10 % favors a diagnosis of melanoma. CD99 is reported to be expressed in 56 % of spitzoid melanomas in a strong and diffuse pattern but only in 5 % of Spitz nevi. Loss of both cytoplasmic and nuclear expression for p16 is present in spitzoid melanomas as compared with Spitz nevus without any correlation with its Breslow thickness. However, the value of p16 expression has been recently questioned as loss of p16 staining does not necessarily reflect malignancy, at least in spitzoid melanoma of adulthood type. Neuropilin-2 is a cytoplasmic/cell surface protein that is a mediator of melanoma-endothelial cell interaction and has been found to be expressed by spitzoid melanoma, while most Spitz nevi are negative. A wider number of cases and a long-term follow-up are needed to determine whether immunohistochemistry has any predictive value in the evaluation of spitzoid lesions.

As for molecular diagnostic studies, spitzoid tumors and melanoma usually show different genetic profiles. Chromosomal aberrations were detected in a higher percentage of cases of spitzoid melanoma by FISH analysis, but this finding deserves further validation. Recently, increased sensitivity for detection of malignant spitzoid neoplasms using 9p21 FISH has been described, and cases with homozygous 9p21 deletions seem to have the greatest risk of malignant biological behavior.

Array comparative genomic hybridization (aCGH) has demonstrated that 76 % of Spitz nevi had no DNA copy changes, while the remaining subset had a gain involving the entire p-arm of chromosome 11 corresponding to expression of the HRAS gene. On the other hand, HRAS is rarely mutated in malignant melanoma, which in contrast can have multiple copy gains in chromosomes 7, 8, 6p, and 1q and/or deletions in chromosomes 9p, 10q, 6q, and 8p (22 %) and can have mutations in B-RAF and N-RAS.

Differential Diagnosis

Clinically, spitzoid melanoma resembles hemangioma, pyogenic granuloma, xanthogranuloma, or basal cell carcinoma. The histopathologic spectrum of spitzoid melanocytic proliferations includes typical Spitz nevus, Spitz tumor, atypical Spitz tumor, and spitzoid melanoma arising de novo. There is no single specific criterion and the diagnosis relies on a good clinical, histopathologic, immunohistochemical, and molecular profile correlation (see section "Pathology"). Lesions that cannot be definitively classified are referred to as atypical spitzoid neoplasms that are a provisional diagnostic category rather than a definitive diagnosis.

Prognosis

The prognosis of spitzoid melanoma is the same as that for other variants of melanoma of equal Breslow thickness. However, the prognosis seems also to be related to the age of the patient; in fact, children aged 17 years or younger with spitzoid melanomas have a better prognosis than adults, even when they have local metastases. The hypothesis that spitzoid melanomas in childhood and adulthood are biologically different deserves further studies. The 5-year survival rate was 88 % when arising in patients between age 0 and 10 years compared with 49 % in patients aged 11–17 years.

Treatment

Spitzoid melanoma must be treated following the same guidelines as for other types of melanoma, which is based on Breslow tumor thickness, ulceration, and mitotic figures. Melanomas in situ must be excised with 0.5 cm margin of noninvolved skin; for invasive melanomas of less than 1 mm in thickness, the margin is 1 cm; for 1–2 mm in thickness, the margin is 1–2 cm; and for melanomas 2–4 mm in thickness, the recommended margin is 2 cm. As for sentinel lymph node biopsy (SLN), spitzoid melanoma follows the same

guidelines as the other types of melanomas. The SLN biopsy is only for prognostic purposes and is not intended to be therapeutic. If the SLN is positive, complete lymph node dissection is performed.

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Nested Melanoma of the Elderly

53

Franco Rongioletti

Introduction

Nested melanoma of the elderly (NME) is a new histopathologic variant of superficial spreading melanoma, characterized by a horizontal spread of intraepidermal large nests mimicking a benign junctional nevus.

Clinical Features

NME is a flat, irregularly pigmented and shaped lesion measuring 5–10 mm in diameter, on heavily sun-damaged skin in a patient older than 60 years (Fig. 53.1).

Dermatoscopic examination shows the presence of variably pigmented and irregularly distributed globules (Fig. 53.2), irregular blotches, and sometimes atypical pigment network, and confocal microscopy reveals the presence of a "cloud" pattern composed of large compact nests with variable atypia that is indicative of melanoma.

Pathology

The architectural pattern is very similar to that of a junctional or superficial compound nevus (Fig. 53.3). The melanocytes are mostly grouped in distinct nests of the same size and shape and regularly distributed along the dermoepidermal junction (Fig. 53.4). There is variable cytologic atypia and only few, if any, melanocytes spreading throughout the epidermis associated with a lentiginous pattern (Fig. 53.5). The histological clues for diagnosis are the unusual findings of bizarre, large junctional nests in an old patient who should not have junctionally active nevi anymore and the presence of solar elastosis. FISH assay targeting RREB1, MYB, Cep6, and CCND1 has revealed chromosomal aberrations consistent with the standardized FISH diagnostic criteria for melanoma, and aCGH has identified multiple genomic aberrations.

Differential Diagnosis

NME can be diagnosed as junctional or compund nevus if proper attention is not paid to the age of patient, actinic elastosis and architectural and cytologic atyoia.

Prognosis

The biological behavior is not aggressive as these tumors are either in situ melanoma or thin melanoma less than 1 mm of thickness.

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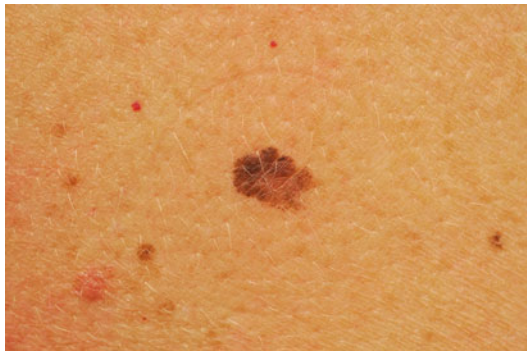

Fig. 53.1 Nested melanoma of the elderly. A flat, irregularly pigmented and shaped lesion measuring 8 mm in a 65-year-old man

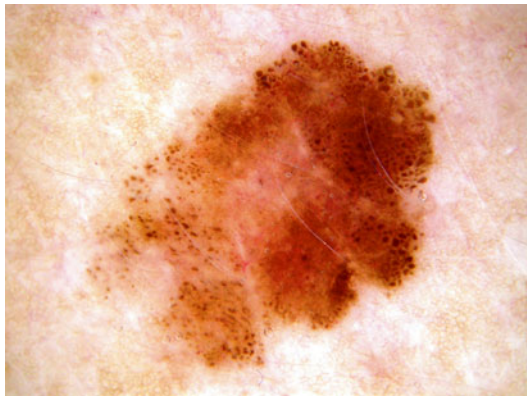

Fig. 53.2 Nested melanoma of the elderly. Dermatoscopic examination shows the presence of irregularly distributed globules

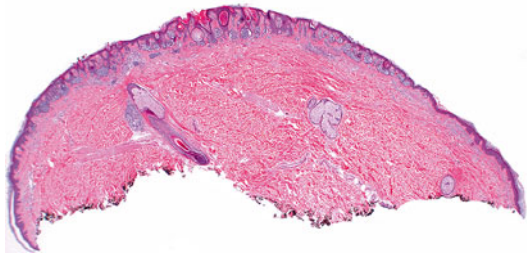

Fig. 53.3 Nested melanoma of the elderly. The architectural pattern is very similar to that of a superficial compound nevus with a lentiginous pattern

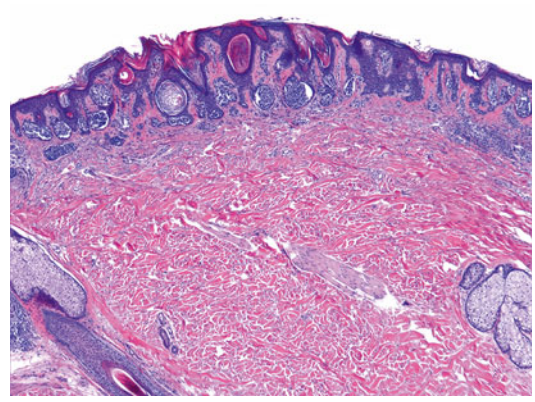

Fig. 53.4 Nested melanoma of the elderly. The melanocytes are mostly grouped in distinct nests of the same size and shape and regularly distributed along the dermoepidermal junction

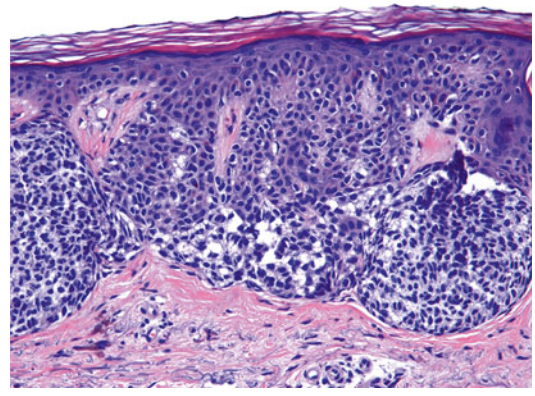

Fig. 53.5 Nested melanoma of the elderly. The histological clues for diagnosis are the unusual findings of bizarre, large junctional nests in an old patient and the presence of solar elastosis. There is variable cytologic atypia and only few if any melanocytes spreading throughout the epidermis

Treatment

NME must be treated following the same guidelines as for other types of melanoma.

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Malignant Blue Nevus

54

Elisa Cinotti and Franco Rongioletti

Introduction

Malignant blue nevus (MBN) is a subtype of melanoma. This term was first coined by Allen and Spitz to denote tumors that resembled blue nevi morphologically (blue color and pigmented dendritic melanocytes) but resulted in metastasis and patient death. The term is now used in three circumstances: malignant transformation or melanoma in a preexisting blue nevus, melanoma with architectural or cytologic features resembling cellular blue nevus but apparently arising de novo, or melanoma with an admixed, residual benign cellular blue nevus component. Martin et al. advocated the term blue nevus-like or associated melanoma because MBN can lead to confusion representing an oxymoron (the adjective "malignant" is coupled with the noun "nevus" that connotes a benign tumor).

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Clinical Features

MBN presents as a bluish nodular lesion (Fig. 54.1). Dermatoscopic features have been described in a case and consisted of black blotches and bluish reticular-like formations. MBN occurs more commonly in men, typically in the fourth decade, and can occur anywhere in the body, with a predilection for the scalp. The mean size is 2.9 cm (range, 1–4 cm). The history usually includes recent enlargement or change in a previously stable blue nevus. The vast majority of MBN are melanoma associated with a cellular blue nevus.

Pathology

MBN are often large (usually >2–3 cm), asymmetrical nodular, or multinodular tumors characterized by a proliferation of spindle, fusiform, or ovoid, pigmented cells, melanophages, and stromal sclerosis in the dermis and often the subcutis (Fig. 54.2). By definition, there is sparing of the epidermis. Epithelioid malignant melanocytes are often a conspicuous component and a useful clue for diagnosis in association with frankly malignant cells, mitotic figures (approximately 1–2 mitoses/mm^2), vascular invasion, expansive or destructive growth, marked cytologic atypia, infiltrative margins, and often widespread necrosis (Figs. 54.3, 54.4, 54.5, 54.6 and 54.7). Melanocytic immunohistochemical markers are

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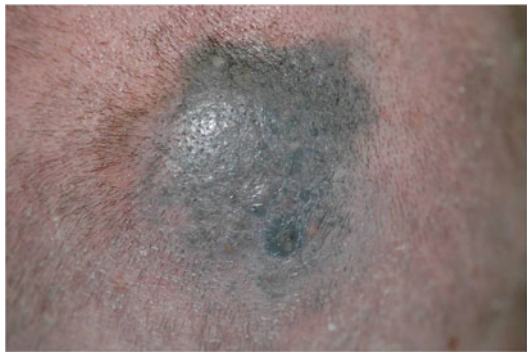

Fig. 54.1 Malignant blue nevus. A bluish fast-growing nodular lesion on the scalp

Fig. 54.2 Malignant blue nevus. A strongly pigmented asymmetrical proliferation involving the dermis and the subcutis sparing the epidermis (courtesy of Carlo Tomasini, Turin, Italy)

expressed. aCGH analysis has failed to show loss of heterozygosity for a number of genes operative in melanomagenesis, such as MTS1, MX11, CMM1, p53, NF1, L-myc, hOCG1, and MCC.

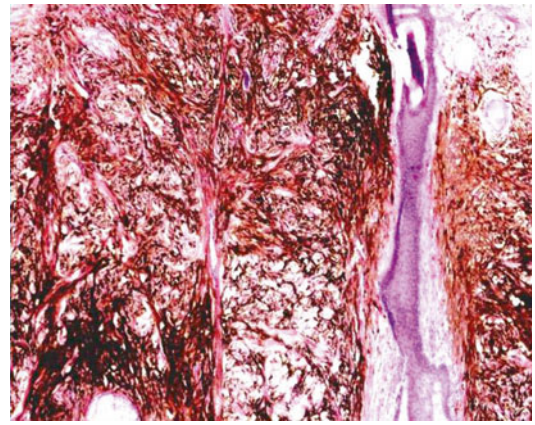

Fig. 54.3 Malignant blue nevus. In this area, the tumor is composed of spindle, fusiform pigmented cells and melanophages mimicking a blue nevus

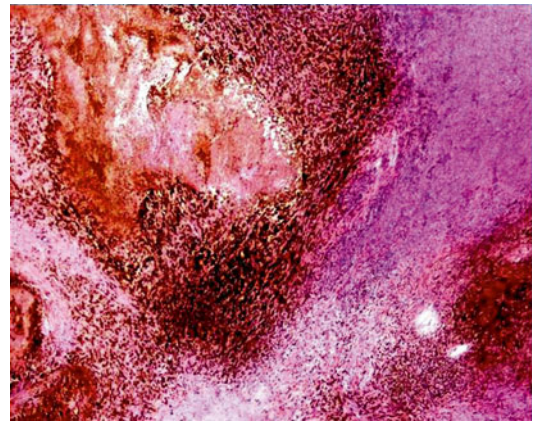

Fig. 54.4 Malignant blue nevus. In this area, the tumor shows an expansive and destructive growth pattern with deeply pigmented cells, melanophages, clear cells, and widespread necrosis

Differential Diagnosis

MBN can generally be distinguished from blue nevus by the presence of a frankly malignant component. Although rare, blue nevi may involve lymph nodes. In this case, the lymph node capsule or intranodal fibrous trabeculae are involved, in contrast to metastatic melanoma (including MBN) that usually involves the subcapsular sinus region of lymph nodes and exhibits nuclear enlargement, pleomorphism, and mitotic activity.

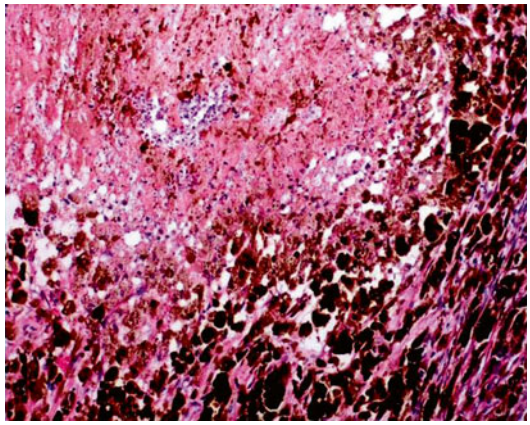

Fig. 54.5 Malignant blue nevus. Area of necrosis surrounded by pigmented cells, melanophages, and dendritic cells

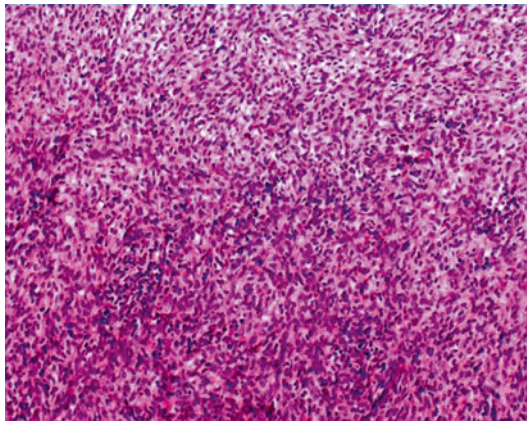

Fig. 54.6 Malignant blue nevus. Elongated spindle cells reminiscent of cellular blue nevus

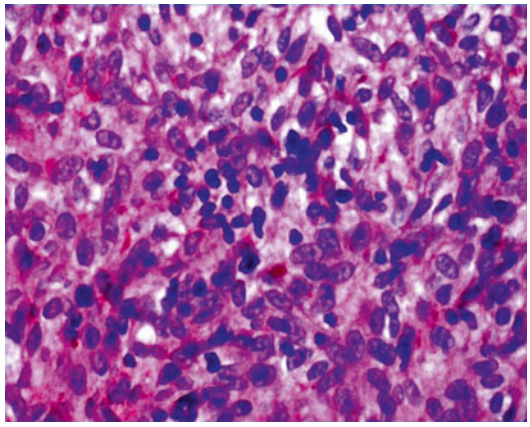

Fig. 54.7 Malignant blue nevus. Epithelioid malignant melanocytes with dendritic cells and mitotic figures

The differential diagnosis with the atypical cellular blue nevus (ACBN), an intermediate category of blue nevus taking part to the melanocytic tumors of uncertain malignant potential (MELTUMP), is difficult. In ACBN, areas of cellular pleomorphism, multinucleated cells, and atypical mitoses can be present, and even experienced dermatopathologists have considerable difficulty distinguishing ACBN from MBN. For some authors, ACBN does not exist and should be classified as blue nevus or melanoma.

Cutaneous metastases from melanoma rarely mimic MBN, and when they lack atypical features, they may mimic blue nevus. However, correlation with the clinical features is critical to establishing the correct diagnosis.

Prognosis

Given the relatively small numbers of patients reported in the literature, the prognosis of MBN is poorly understood. The common prognostic factors that are assessed in melanoma should be applied to MBN. Usually, MBN has considered to carry a less favorable prognosis than that of conventional melanoma with a metastasis rate of up to 83 % and a mortality rate of 67 ~ 73 %. However, the adverse prognosis seems to be linked more to a delay of diagnosis.

Treatment

The treatment is the same of conventional melanoma, with early wide surgical excision. Sentinel node biopsy is recommended because, according to the limited data available in the literature, lymph nodes are often involved.

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Clear Cell Sarcoma of Soft Tissue (Malignant Melanoma of Soft Tissue)

55

Elisa Cinotti and Franco Rongioletti

Introduction

Clear cell sarcoma (CCS) of the soft tissue is an exceedingly rare sarcoma with melanocyte differentiation and a distinct genetic background whose precise lineage remains unclear. Usually, it is a tumor of deep soft tissue, but a primitive cutaneous localization has been described by Hantschke et al. in 2010 (cutaneous clear cell sarcoma).

Clinical Features

Typically, CCS of soft tissue is observed as a slowly growing deep soft tissue tumor, affecting the extremities of adolescents or young adults, especially around the ankle and foot, attached to tendons or aponeuroses. Rarely, it can be a primitive cutaneous tumor. Other possible rare sites are the oral mucosa, gastrointestinal tract, kidney, and bone. The gender distribution between males and females is equal.

Pathology

CCS of soft tissue is characterized by uniform nests and fascicles of spindled or slightly epithelioid cells with finely granular eosinophilic or clear cytoplasm with large nuclei and prominent nucleoli, separated by delicate fibrous septa of hyaline collagen (Figs. 55.1 and 55.2). Multinucleated wreath-like giant cells are present in more than 50 % of cases. The cutaneous variant can be confined to the dermis or invade the subcutis. Sometimes it spreads up to the epidermis mimicking junctional nests. Melanin pigment is not always evident; necrosis and ulceration are variable.

Immunohistochemical studies show that in most cases, the neoplastic cells express melanocytic markers, i.e., S-100 protein, HMB45, melan-A (Fig. 55.3a, b), and microphthalmia transcription factor (MiTF). Neural, neuroendocrine, or epithelial antigens are sometimes expressed and some tumors have melanosomes.

The karyotype shows a characteristic reciprocal translocation t(12;22)(q13;q12) that results in the fusion gene *EWS/ATF* and more rarely the translocation t(2, 22) (q34; ql2) that results in the fusion gene *EWSRI/CREBI*. These translocations may be identified by fluorescence in situ hybridization (FISH). Fusion type is not related to biological behavior.

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Differential Diagnosis

CCS of soft tissue can easily be confused with a dermal variant of spindle cell malignant melanoma or with a metastasis of malignant melanoma because it shows the immunohistochemical profile of malignant melanoma. However, clear cell melanoma is characterized by fascicles of uniform population of tumor cells encased by delicate fibrous septa, a pattern that is seldom observed in malignant melanoma. Moreover, CCS does not display any increase in melanocytes within the epidermis or pagetoid spread of atypical melanocytes and shows multinucleated giant cells with characteristic multiple peripherally placed nuclei. Ultimately, it is characterized by a typical recurrent chromosomal translocation t(12;22)(q13;q12) that is not present in malignant melanoma and can be demonstrated by FISH analysis (Fig. 55.4) and lack melanoma-associated BRAF mutations.

Other differential diagnoses include spindle cell squamous carcinoma, cutaneous leiomyosarcoma, atypical fibroxanthoma, paraganglioma-like dermal melanocytic tumor, clear cell myelomonocytic tumor, perivascular epithelioid cell tumor (PEComa), malignant peripheral nerve sheath

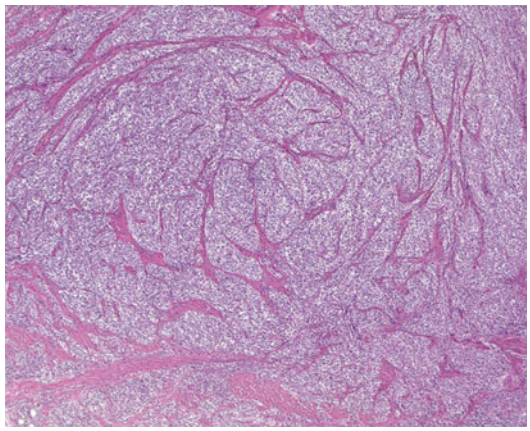

Fig. 55.1 Clear cell sarcoma of soft tissue. The neoplasm is characterized by uniform nests and fascicles separated by delicate fibrous septa of hyaline collagen

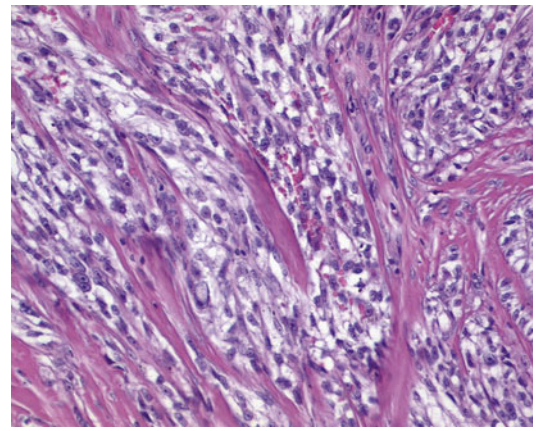

Fig. 55.2 Clear cell sarcoma of soft tissue. The nests are composed of spindled or slightly epithelioid cells with finely granular eosinophilic or clear cytoplasm with large nuclei and prominent nucleoli

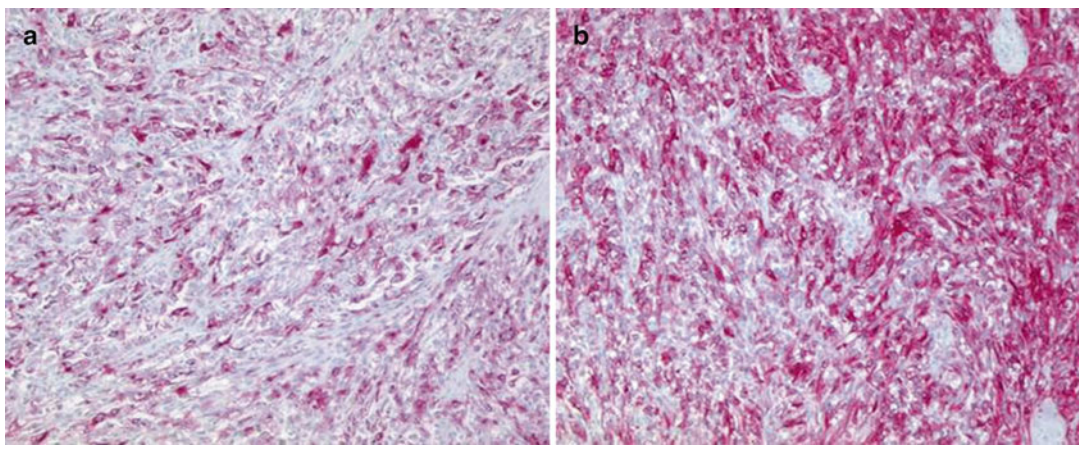

Fig. 55.3 Clear cell sarcoma of soft tissue. (**a**) The cells are positive for melan-A and (**b**) for HMB45

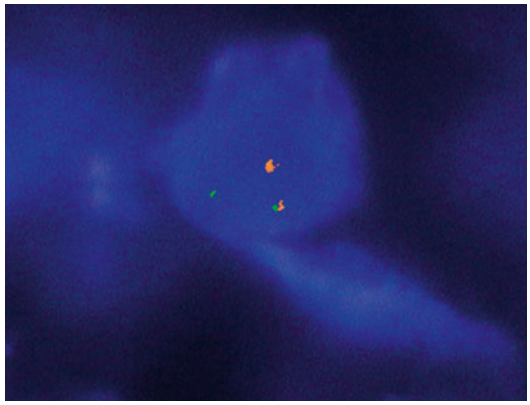

Fig. 55.4 Clear cell sarcoma of soft tissue. The typical recurrent chromosomal translocation t(12;22)(q13;q12) demonstrated by FISH analysis (Courtesy of Heinz Kutzner, Friedrichschafen, Germany)

tumor, and synovial sarcoma. A careful histological evaluation coupled with immunohistochemical demonstration of melanocytic differentiation in CCS usually establishes the diagnosis.

Prognosis

CCS is associated with poor overall survival. Metastasis occurs mainly to the regional lymph nodes, lungs, and bones. With current treatment, the 5-year survival is 40–67 %.

Treatment

The mainstay of treatment is wide excision of the tumor. The use of sentinel lymph node biopsy may become an important procedure in detecting occult regional metastasis and guiding the extent of surgery. The beneficial effects of adjuvant chemotherapy and radiotherapy have not been fully evaluated.

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Part XI

Neuroendocrine, Neuroectodermal and Nervous Tumours

Merkel Cell Carcinoma

56

Elisa Cinotti and Franco Rongioletti

Introduction

Merkel cell carcinoma (MCC) is a rare, primary, highly malignant cutaneous neoplasm with epithelial and neuroendocrine differentiations that predominantly occurs in fair-skinned, elderly Caucasians and immunocompromised patients. It was first described in 1972 by Cyril Toker as a trabecular carcinoma. The true origin is unknown. Until recently, Merkel cells were believed to be at the origin of MCC, but recent studies show that MCC are more likely to arise from epidermal stem cells. The exact etiology is not known, but is postulated to relate to sunlight, immunosuppression, and infection by a Merkel cell polyoma virus. In fact, the frequent detection of the virus in the tumor (70–90 %), its monoclonal integration in the tumor cells, and the expression of viral oncogenes highly suggest that the virus is causally linked to the pathogenesis of MCC cases.

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Clinical Features

MCC presents as an asymptomatic, firm, skin-colored, reddish, bluish, or purple tumor of the skin (Fig. 56.1). Size at the time of first consultation is usually smaller than 2 cm, although MCC is characterized by rapid growth. The incidence is of 0.6 per 100.000, and it is increasing. The head and neck area is the most frequently affected site (50 %), followed by the extremities (40 %), trunk, genitalia, and unknown primary sites (10 %). MCC occurs mostly in white elderly with a male/female ratio of 2.3:1. About 78 % of patients are older than 59 years. However, MCC may occur at a younger age in immunosuppressed patients such as HIV-positive subjects and organ transplant recipients. The risk of MCC is significantly increased in patients with other malignancies, especially B-cell malignancies.

TMCC can be staged as follows:

Stage I – Primary tumors ≤2 cm, without evidence of regional lymph node involvement

Stage II – Primary tumors >2 (T2 or T3) or a primary tumor with invasion into the bone, muscle, fascia, or cartilage (T4)

Stage III – Any primary tumor with regional lymph node disease

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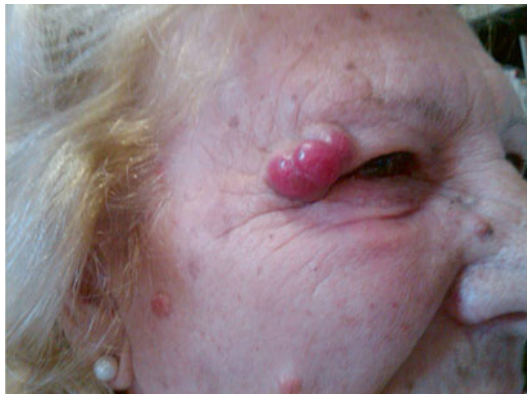

Fig. 56.1 Merkel cell carcinoma. An asymptomatic, firm, purple tumor on the face of an old patient

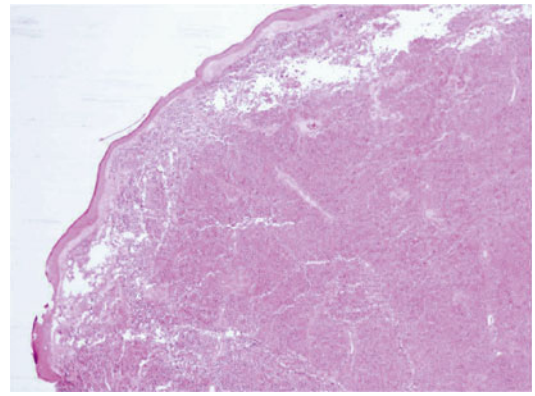

Fig. 56.2 Merkel cell carcinoma. A dermal bluish nodule made up of densely packed cells

Stage IV – Metastasis beyond the regional lymph nodes, regardless of the status of the primary tumor and regional nodes

Pathology

MCC usually appears as a dermal nodule (Fig. 56.2), which frequently extends into the subcutaneous fatty tissue. The tumor cells are small, blue, round to oval, and of uniform size, with basophilic nucleus and minimal cytoplasm (Fig. 56.3). Nuclear membranes are distinct, the chromatin is finely dispersed, and nucleoli are usually inconspicuous; mitoses and apoptotic bodies are numerous (Fig. 56.4). Tumor cells may be focally spindled and rarely large, especially in recurrences after radiotherapy. Epidermotropism of tumor cells is uncommon, and in exceptional cases, the tumor cells are entirely limited to the epidermis. Ulceration of the epidermis occurs in a subset of cases. The papillary dermis and adnexa are usually spared.

Three patterns have been recognized: the trabecular cell type seen in 25 % of cases in which the cells are arranged in interconnected trabeculae separated by strands of stromal tissue; the intermediate cell type, observed in over 50 % of patients, in which large nest of cells without organoid architecture are recognized with a better prognosis compared to the other ones; and the small cell type, the least common one, where

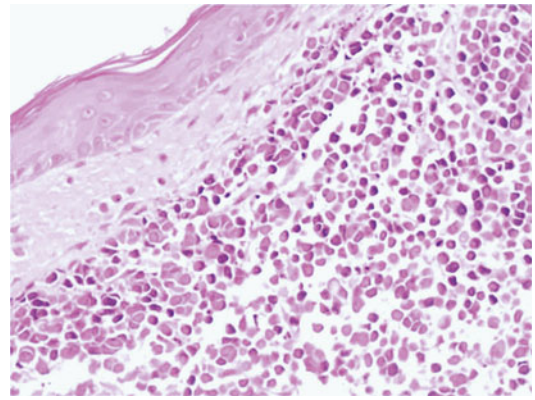

Fig. 56.3 Merkel cell carcinoma. The tumor cells are small, round to oval, and of uniform size, with basophilic nucleus and minimal cytoplasm

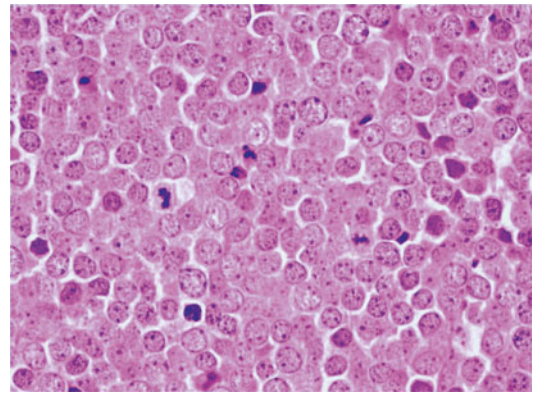

Fig. 56.4 Merkel cell carcinoma. Nuclear membranes are distinct, the chromatin is finely dispersed, and nucleoli are usually inconspicuous, while mitoses are numerous

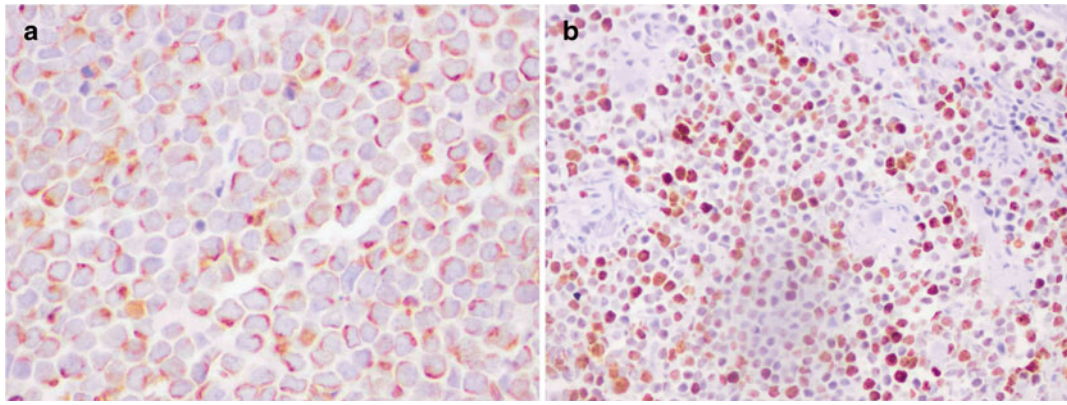

Fig. 56.5 Merkel cell carcinoma. (**a**) Tumor cells are positive for cytokeratin 20 with the typical paranuclear dot pattern, and (**b**) the Ki-67 proliferation index is very high

solid sheets and clusters of cells separated by abundant stroma with large areas of necrosis are seen. Additional pattern include: squamous, melanocytic, eccrine, leiomyosarcomatous, rhabdomyoblastic, and fibrosarcomatous differentiation.

Larger lesions may show angiolymphatic involvement and scattered or dense infiltrate of lymphocytes and sometimes plasma cells. Vascular proliferation is present in approximately 20 % of cases. The concurrence of MCC and squamous cell carcinoma or Bowen's disease is also documented.

MCC shows epithelial and neuroendocrine differentiation. Tumor cells express low-molecular-weight cytokeratins (detectable by specific or broad-spectrum cytokeratins such as AE1/AE3, CAM5.2), epithelial membrane antigen, and the epithelial marker Ber-EP4. Positive staining for anti-cytokeratin 20 (CK20) is quite sensitive (Fig. 56.5a); in fact, CK20 is expressed by 97 % of MCC.

The staining pattern for low-molecular-weight cytokeratins and CK20 typically consists of paranuclear dots but may also be cap-like paranuclear or diffuse cytoplasmic staining. Markers of neuroendocrine differentiation include chromogranin, synaptophysin, neuron-specific enolase (NSE), bombesin, somatostatin, calcitonin, and gastrin. Merkel cell carcinoma also expresses CD117. The Ki67 proliferation index evaluated with Ki67 is high (Fig. 56.5b). Ultrastructural studies reveal the presence of dense core neurosecretory granules, tightly packed intermediate filaments, and desmosomes in the proliferating cells.

Cytogenetic analysis has showed many different chromosome abnormalities, in particular deletion of 1p35-36 has been found in 40 % of examined cases. Mutations in tumor suppressor genes may also be present including p73 as well as a loss of heterozygosity in chromosome 3p21, a region that is also affected in many cases of small cell cancer of the lung. However, the relationship of these genetic changes to prognosis and therapeutic outcomes is far to be clear.

Differential Diagnosis

Clinical differential diagnoses include hemangioma, angiosarcoma, and lymphoma. The "small round blue cell" histological pattern of MCC must be differentiated from basal cell carcinoma, eccrine carcinoma, poorly differentiated squamous cell carcinoma, lymphoma, small cell melanoma, metastatic neuroblastoma, primary peripheral primitive neuroectodermal tumor, and metastatic neuroendocrine carcinoma such as small cell lung carcinoma. Immunohistochemical staining is required to make a correct differential diagnosis: MCC is positive for epithelial and neuroendocrine markers but is negative for lymphoid (leukocyte common antigen) and melanoma (HBM45 and S-100) markers. Small cell

carcinoma of the lung can be positive for CK20 (<10 % of cases), but it can be distinguished from MCC for the expression of the thyroid transcription factor-1 (TTF-1) and the absence of the neurofilament protein (NFP).

Prognosis

MCC biological behavior is highly aggressive with high rates of local recurrences, regional lymph node metastasis, and hematogenous and/or distant lymphatic spread and metastasis.

The 5-year survival rate ranges from 30 % to 64 % and is strongly dependent on the presence of regional and distant metastasis, with a far worse outcome in advanced stages of disease. A recent single institution study shows 5-year MCC-specific survival rates of 87 %, 63 %, 42 %, and 0 % for stages I, II, III, and IV, respectively.

Negative prognostic markers are the male gender, the head and neck localization, the size >2 cm, and the immunosuppression and lymph node involvement.

Treatment

Early wide surgical excision of the tumor with a margin of at least 1–2 cm is the treatment of choice. Sentinel node analysis is recommended. Adjuvant radiotherapy is recommended to the resection site especially for lesions thought to be at increased risk of local recurrence (close or positive margin, tumor ulceration, deep invasion, large size, and lymphovascular invasion). The role of adjuvant chemotherapy is controversial. For metastatic tumors, cisplatin or carboplatin plus etoposide or doxorubicin can be used. Response rates of up to 40 % were observed in some studies; however, those who responded did so only for a short time. New promising treatments could be multitargeted tyrosine kinase inhibitors (pazopanib, imatinib).

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Primary Cutaneous Ewing Sarcoma/Primitive Neuroectodermal Tumor

57

Jerad M. Gardner and Bruce R. Smoller

Introduction

Ewing sarcoma/primitive neuroectodermal tumor (ES/PNET) is a family of very similar "small round blue cell" tumors that typically occur in the bone or soft tissue of children and young adults. Although historically these tumors were often subdivided into distinct diagnostic entities on the basis of clinical and histological variations, they are now all regarded as a single entity in light of molecular and immunohistochemical findings. ES/PNET occurring as a primary skin tumor is rare with fewer than 50 cases reported in the literature mainly as case reports and several small case series.

Clinical Features

Primary cutaneous ES/PNET, like its counterparts in bone and deep soft tissue, is more common in children and adolescents, although it may also occur in adults. Some, but not all, studies have shown a female sex predilection. It may present as a benign-appearing skin nodule or pedunculated/polypoid mass and is usually relatively small (3 cm or less) although larger examples have been reported. It may occur at a wide variety of anatomic sites.

Pathology

By definition, the tumor must be confined to the dermis, subcutis, or both without involvement of deep soft tissue (Fig. 57.1). The histological features are similar to those of skeletal and deep soft tissue ES/PNET. The tumor presents as a nodular, densely cellular proliferation centered in the dermis or subcutis composed of sheets of cells with monotonous oval or round nuclei, vesicular chromatin, and indistinct nucleoli (Figs. 57.2, and 57.3). The cells have a minimal amount of clear or pale cytoplasm. Homer-Wright pseudorosettes may rarely be seen. Mitotic figures may be rare or abundant, but pleomorphism is typically not present. The tumor cells usually contain abundant glycogen on a PAS stain without diastase. By immunohistochemistry, the tumor cells display strong diffuse membranous expression of CD99 (the protein product of the *MIC2* gene) (Fig. 57.4), variable nuclear expression of FLI-1, and, rarely, focal staining for S-100 protein, cytokeratin, or neuron-specific enolase. The tumor cells are negative for diffuse S-100 protein, diffuse keratin, cytokeratin 20, HMB45, melan-A,

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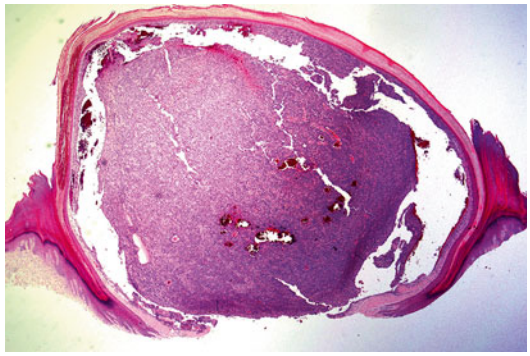

Fig. 57.1 Primary cutaneous ES/PNET displays a nodular dermal-based proliferation of small round blue cells (Image courtesy of Steven D. Billings, MD)

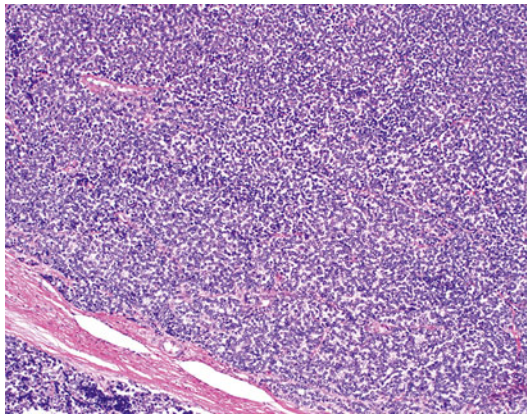

Fig. 57.2 ES/PNET is composed of hypercellular sheets of monotonous oval/round cells

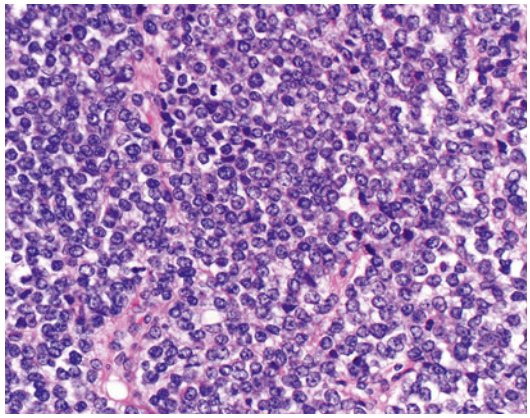

Fig. 57.3 The tumor cells have round to oval nuclei, vesicular chromatin, and minimal cytoplasm. Multiple mitoses are present

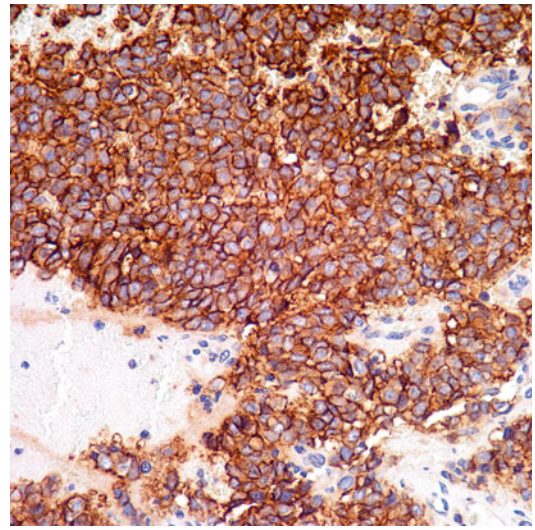

Fig. 57.4 Strong diffuse membranous expression of CD99 is characteristic of ES/PNET

smooth muscle actin, desmin, myeloperoxidase, CD45, CD3, CD20, CD79a, CD10, TdT, chromogranin, and synaptophysin. Like other ES/PNET, primary cutaneous ES/PNET is characterized by a balanced translocation between the *EWS* gene on chromosome 22 and one of several potential fusion partner genes including *FLI1* (most common), *ERG,* and *ETV1* on chromosomes 11, 21, or 7, respectively. The translocation may be detected either by fluorescence in situ hybridization (FISH) utilizing a dual-color breakapart probe for the *EWS* gene or by reverse transcriptase polymerase chain reaction (RT-PCR) targeting the various chimeric fusion genes that result from balanced translocation of *EWS.* However, not all examples of primary cutaneous ES/PNET in the literature had detectable translocations, perhaps due to either technical difficulties in the analysis of small samples or due to the presence of not yet identified variant translocation partners.

Differential Diagnosis

The most important differential diagnoses to exclude are cutaneous metastasis of ES/PNET and cutaneous extension of a deep soft tissue ES/PNET; both require clinical and radiologic

correlation. Additionally, the histological differential diagnosis for primary cutaneous ES/PNET is quite broad and includes other "small round blue cell" tumors that may be present in the skin and subcutis such as neuroblastoma, embryonal or alveolar rhabdomyosarcoma, lymphoblastic lymphoma, leukemia cutis, carcinoma (poorly differentiated adnexal carcinoma including malignant trichoblastic neoplasms, Merkel cell carcinoma, metastatic small cell carcinoma, other neuroendocrine carcinomas), small cell melanoma, desmoplastic small round cell tumor, or poorly differentiated synovial sarcoma. A combination of immunohistochemistry and molecular analysis can usually exclude these entities and confirm the diagnosis of ES/PNET. It is worth noting that while strong diffuse membranous expression of CD99 is a highly sensitive marker of ES/PNET, it is not entirely specific; CD99 expression may be seen in many other small round blue cell tumors. Additionally, while RT-PCR may specifically confirm the presence of an ES/PNET-specific gene rearrangement, FISH showing *EWS* gene rearrangement is not entirely specific for ES/PNET, as the *EWS* gene may be rearranged in a variety of other neoplasms including myoepithelioma, myoepithelial carcinoma, desmoplastic small round cell tumor, clear cell sarcoma, and angiomatoid fibrous histiocytoma among others. Correlation with clinical and histological features is essential when interpreting the results of molecular analysis.

Prognosis

The prognosis of primary cutaneous ES/PNET appears to be markedly favorable in comparison to skeletal or deep soft tissue ES/PNET. The majority of patients in published case series did not develop either local recurrence or distant metastasis, and the vast majority were alive with no evidence of disease at the time of last follow-up. Only two patients in the literature developed distant metastases and subsequently died of disease, and one patient developed regional lymph node metastasis but was still alive after 8 years.

Treatment

As this is a rare tumor, there is no standardized treatment for primary cutaneous ES/PNET. It is often treated by surgical excision sometimes coupled with chemotherapy and/or radiotherapy. Some children have been treated according to the ES/PNET-specific treatment protocols that are utilized in skeletal or deep soft tissue ES/PNET. In light of the excellent prognosis of this tumor when confined to the skin, some authors have suggested that surgical excision should be the primary mode of treatment with adjuvant therapy such as chemotherapy or radiotherapy playing a lesser role; there is limited objective data at this point to firmly support this concept.

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Malignant Peripheral Nerve Sheath Tumor

58

Irina Margaritescu, A. Doru Chirita, and Florina Vasilescu

Introduction

Malignant peripheral nerve sheath tumor (MPNST) is a rare malignant spindle cell tumor derived from components of the nerve sheath such as perineural fibroblasts or Schwann cells. MPNSTs account for 5 % to 10 % of all soft tissue sarcomas. About half of MPNSTs occur in patients with neurofibromatosis type 1 (NF-1) and, in this context, they develop from preexisting plexiform neurofibromas. Sporadic tumors (40 %) develop from medium-sized or large nerve trunks in the proximal extremities or trunk. A few appear after radiation treatment. Pure cutaneous MPNSTs represent very rare variants of MPNSTs predominantly located in the dermis or subcutis. These tumors usually develop in association with a preexisting neurofibroma or small cutaneous nerves and are less commonly associated with neurofibromatosis. Otherwise, skin involvement is usually secondary to local invasion or metastasis from larger underlying tumors.

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Clinical Features

MPNST most commonly appears in adults in the fourth and fifth decades (range 7–89 years). There is no age predilection for cases that occur sporadically. Tumors associated with neurofibromatosis usually appear in younger patients. Cases that occur sporadically have an almost equal sex distribution, whereas those associated with NF-1 have a male predominance. The most common location is the head and neck region, but they also occur in the trunk and extremities. The lesions enlarge slowly over a long period, followed by a rapid growth. The size of the tumors at the time of diagnosis ranges from 2 to 22 cm, with almost half of the lesions over 5 cm in diameter. The diagnosis should be suspected when a previously static tumor in a patient with neurofibromatosis begins to enlarge or becomes painful. The pain may become radicular as the lesion progresses. However, the tumors are not always associated with nerve trunks. Usually, the lesion of MPNST presents as a skin-colored nodule that resembles a neurofibroma but with a rapid

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growth. MPNST may be confused clinically with benign or malignant lesions, such as a cyst, dermatofibroma, neurofibroma, desmoplastic melanoma, or other malignant soft tissue tumors.

Pathology

At low magnification, cutaneous MPNST appears as an unencapsulated tumor that occupies the entire depth of the dermis and extending into the subcutaneous tissue (Figs. 58.1 and 58.2). The tumor consists of irregular interlacing bundles of spindle cells with hyperchromatic, variably pleomorphic wavy nuclei and scanty pale cytoplasm embedded in a collagenous or myxoid stroma. The tumor displays a "marbled" pattern with hypercellular fascicles of spindle cells alternating with hypocellular myxoid areas (Fig. 58.3). Focal areas of perivascular cuffing by tumor cells is a typical feature (Fig. 58.4). Besides the conventional or spindle cell variant, there is an epithelioid variant which is more commonly encountered in cutaneous MPNST. Epithelioid tumors are arranged in sheets of atypical epithelioid cells with round nuclei and pale indistinct cytoplasm. The mitotic activity is an invariable feature (Fig. 58.5). Occasional nuclear palisading

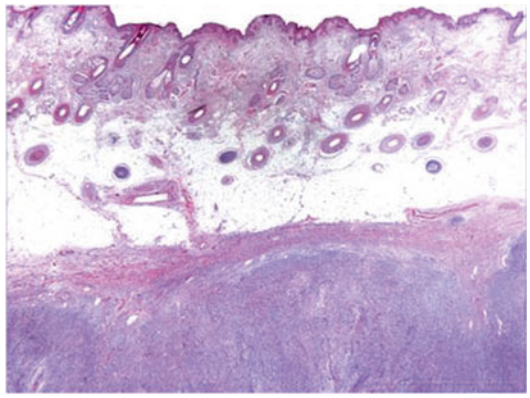

Fig. 58.1 In this case of MPNST, the skin involvement is secondary to local invasion from a subcutaneous tumor

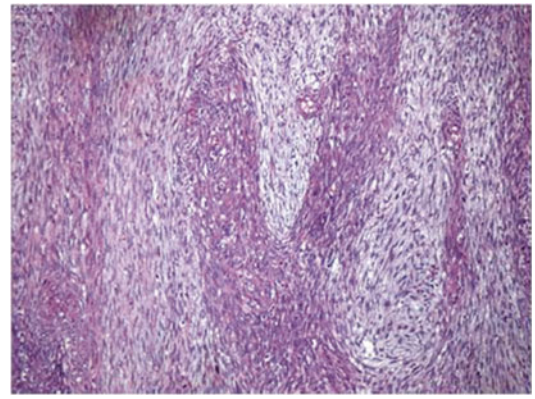

Fig. 58.3 Irregular interlacing bundles of spindle cells display a "marbled" pattern with hypercellular fascicles of spindle cells alternating with hypocellular myxoid areas

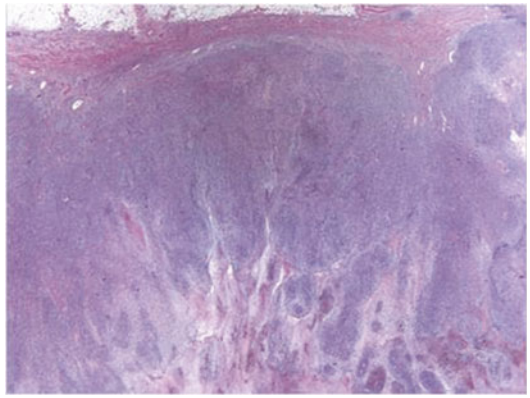

Fig. 58.2 The tumor is large, asymmetrical, and unencapsulated

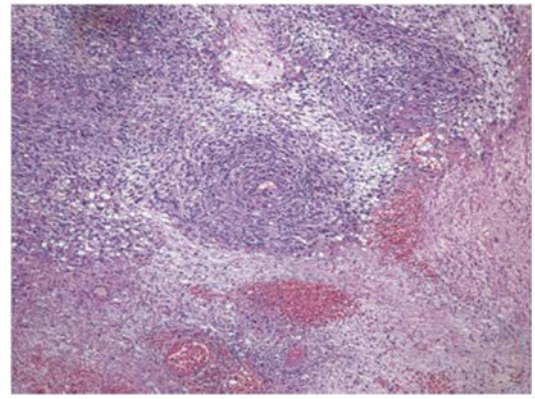

Fig. 58.4 Focal areas of perivascular cuffing by tumor cells is a typical feature

may be seen and multinucleated giant cells have been rarely reported. A rare but characteristic aspect is the presence of hyalinized nodules.

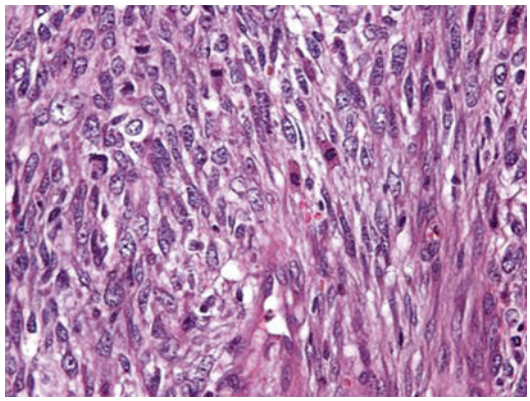

Fig. 58.5 The spindle cells have hyperchromatic, pleomorphic wavy nuclei, with high mitotic activity

Foci of necrosis, hemorrhage, and pseudocystic change may be seen. A storiform or herringbone pattern may be present. Divergent differentiation including foci of chondrosarcoma, osteosarcoma, rhabdomyosarcoma, and angiosarcoma may be apparent. Glandular differentiation can also be encountered. Extremely rare, pigmentation and melanocytic differentiation may be a feature.

MPNST with spindle cell morphology is characterized by a focal and week positivity reaction for S-100. In contrast, the epithelioid variant stains stronger and more uniform with S-100 and is also positive for podoplanin (D2-40). MPNST shows a positive reaction for vimentin, myelin basic protein (MBP), CD56, and CD57 (Leu7) (Fig. 58.6a–c) and a negative reaction for HMB45, melan-A, tyrosinase, microphthalmia transcription factor, smooth muscle actin, and

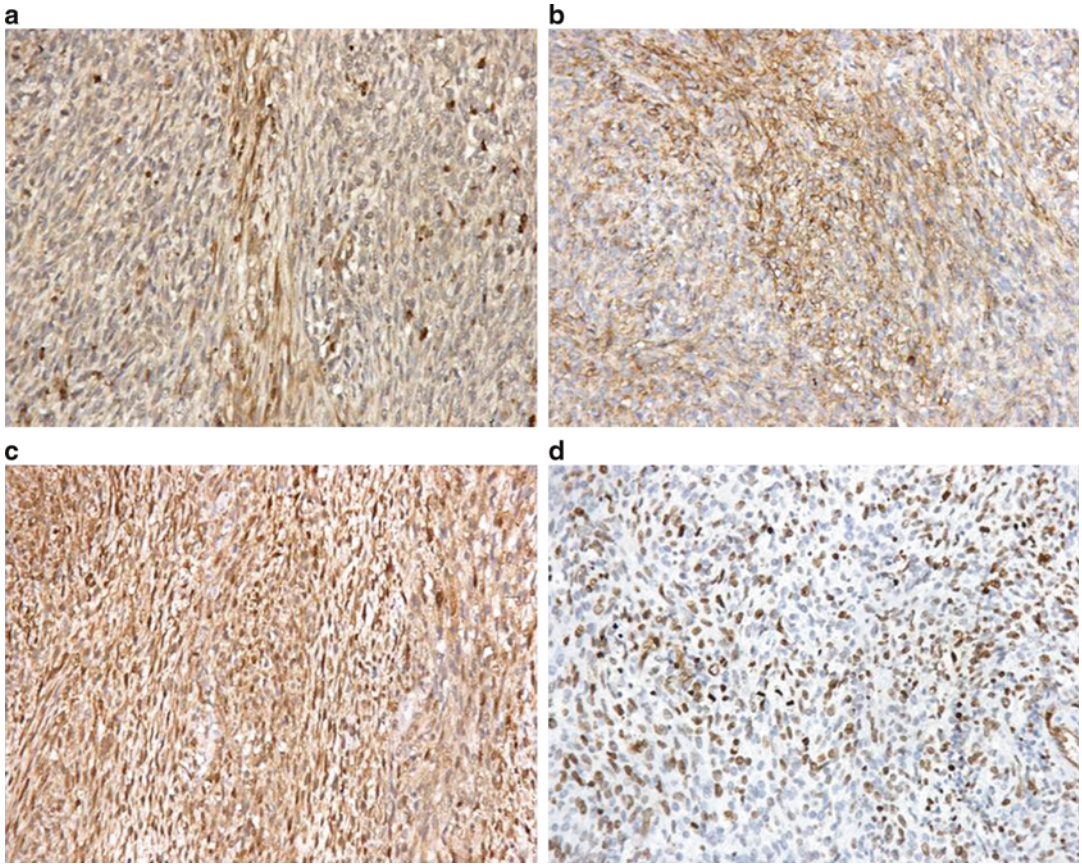

Fig. 58.6 The neoplastic cells are (**a**) focally positive for S-100, (**b**) diffusely positive for CD56, and (**c**) diffusely positive for PGP 9.5 and (**d**) show a high index of proliferation with Ki67

cytokeratin. Proliferative index with Ki67 is high (Fig. 58.6d).

Gains in chromosomes 8q, 17q, and 7p and losses in chromosomes 9p, 11q, and 17p are often found in MPNST. Tumors with gains in chromosome 16p or losses in chromosomes 10q or Xq are associated with poor prognosis.

Differential Diagnosis

The main differential diagnosis includes neurofibroma, schwannoma, and desmoplastic/spindle cell melanoma. Other entities to be considered are benign fibrous histiocytoma, leiomyoma, leiomyosarcoma, dermatofibrosarcoma protuberans, myxofibrosarcoma, and cutaneous metastases from deep-seated sarcomas.

The infiltrative growth pattern, increased cellularity, and frequent mitoses help distinguish MPNST from neurofibroma, schwannoma, dermatofibroma, and leiomyoma.

Distinguishing MPNST from desmoplastic and spindle cell melanoma may be extremely difficult, if not impossible. The presence of lymphocytic aggregates and atypical intraepidermal melanocytic proliferation may help in differentiation of DM from MPNST.

Immunohistochemistry has a limited utility in differentiating DM from MPNST as both neoplasms may be positive for S-100 protein. Moreover, specific melanocytic markers are typically negative in desmoplastic melanoma. However, MPNSTs usually have much less extensive immunoreactivity for S-100 protein. Also, MPNSTs, unlike melanomas, may be positive for CD57 or myelin basic protein. In most difficult cases, the correct diagnosis can be reached only by careful integration of all clinical, pathological, immunohistochemical, and ultrastructural features. A proper panel of antibodies should allow the epithelioid variant of malignant peripheral nerve sheath tumor to be distinguished from metastatic melanoma, metastatic carcinoma, epithelioid sarcoma, epithelioid leiomyosarcoma, and malignant fibrous histiocytoma.

Prognosis

In general, MPNSTs are highly aggressive tumors with rapid invasive growth, tendency to local recurrence, and early hematogenous dissemination, with lungs being the most common site of metastasis. Prognostic factors include: tumor size, tumor location, complete surgical excision, and histological grade. Cutaneous MPNSTs seem to have a better prognosis than their deep-seated counterparts. Possible reasons for this behavior include early clinical detection, accessibility for biopsy, possibility of complete excision with tumor-free margins, and early detection of recurrences.

Treatment

Radical excision with wide margins (≥2 cm) and deep down to the fascia with histological control of resection borders is the standard treatment for MPNST.

Adjuvant radiotherapy may improve local control and reduce local recurrence rates. Adjuvant chemotherapy with ifosfamide-doxorubicin or carboplatin-etoposide–based regimens may be of benefit for patients with unresectable tumors or metastatic disease.

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Part XII

Hematopoietic tumors

Rare Variants of Mycosis Fungoides: Folliculotropic Mycosis Fungoides

59

Irina Margaritescu and A. Doru Chirita

Introduction

Folliculotropic mycosis fungoides (FMF) is a rare variant of MF with distinctive clinical and histological features and a worse prognosis compared to classic MF. Clinically, it present as pruriginous follicular papules, acneiform and cystic lesions, and tumid plaques, with or without alopecia, especially on the head and neck region but also on the trunk and extremities. Histologically, it is characterized by an infiltrate of atypical CD4+ T lymphocytes with a propensity to involve pilosebaceous structures usually without evidence of epidermal involvement.

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Clinical Features

FMF affects men more than women, usually in their fifth and sixth decades of life (age range 24–82 years). The disease typically affects the head and neck region, especially the eyebrows and nuchae, but also the trunk and extremities (Figs. 59.1, 59.2, 59.3 and 59.4). Early in the course of disease, FMF may present with very subtle lesions that may be overlooked, like mild perifollicular erythema and subtle patches with follicular prominence, with or without alopecia. Different types of lesions appear in the disease course: keratosis follicularis and acne-like lesions, follicular pustules, milium-like cysts, and prurigo-like nodules (Figs. 59.3 and 59.4). Fully developed and advanced lesions include tumid and infiltrated plaques with or without alopecia, nodules, and tumors. Xanthelasma-like lesions, telangiectatic plaques, annular plaques, leonine facies, and erythrodermas are other rare presentations. Pruritus is a significant feature in most of the cases and sometimes may be extremely severe. The time delay between the onset of the lesions and the diagnosis of FMF is often 3–4 years. FMF may be clinically misdiagnosed as lichen planopilaris, lichen spinulosus, folliculitis, pityriasis rubra pilaris, acne, Favre-Racouchot disease, and lymphomatoid papulosis.

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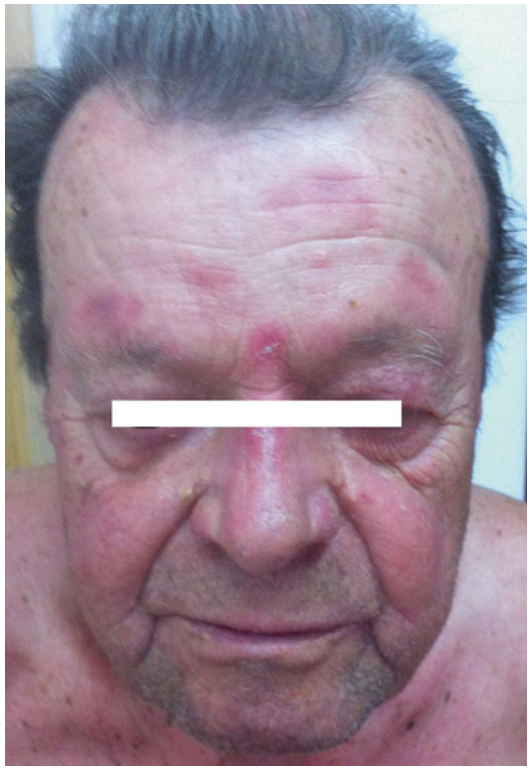

Fig. 59.1 Folliculotropic mycosis fungoides. Intensely pruriginous, dusky erythematous, tumid, alopecic plaques, over the forehead, eyebrows, and eyelids in a 78-year-old man

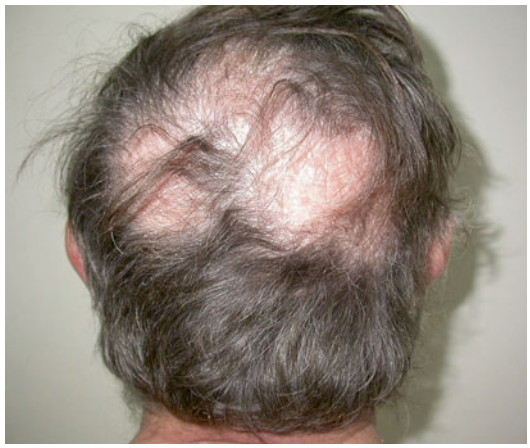

Fig. 59.2 Folliculotropic mycosis fungoides. Infiltrated alopecic plaques on the scalp represent a usual finding in follicular mycosis fungoides

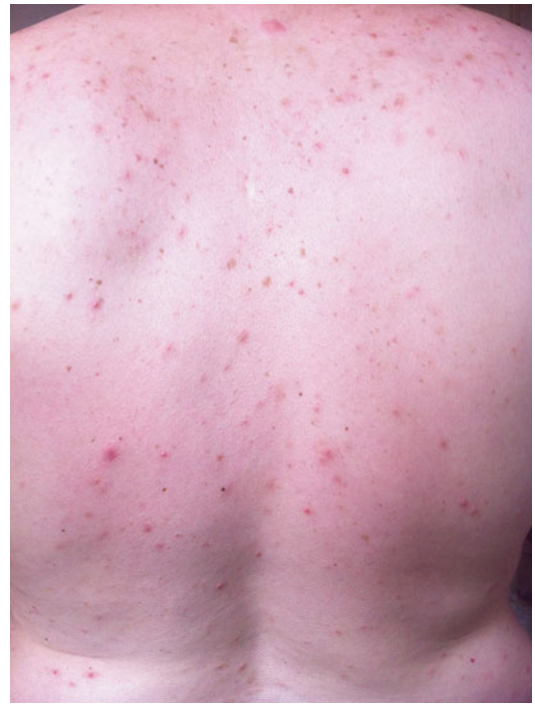

Fig. 59.3 Folliculotropic mycosis fungoides. Subtle widespread acne-like lesions, milium-like cysts, and follicular pustules on the trunk and extremities

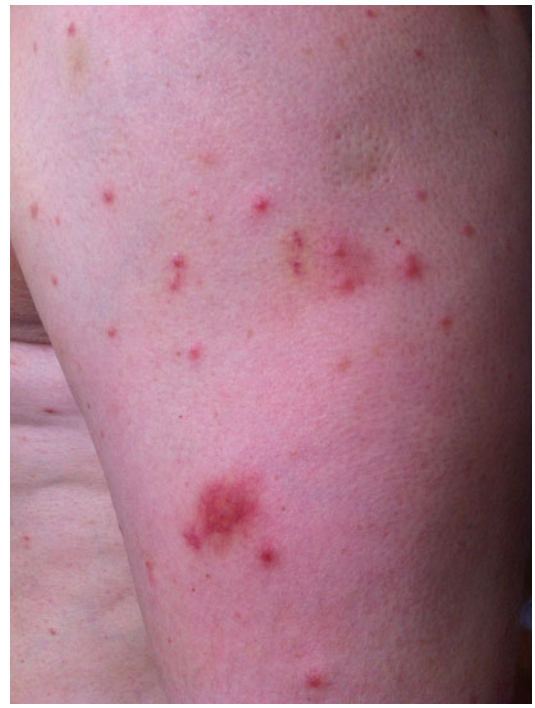

Fig. 59.4 Folliculotropic mycosis fungoides. Follicular papules, pustules, and alopecic plaques are evident on the upper arms

Pathology

As early lesions may not display diagnostic features, biopsies may be misinterpreted as inflammatory processes like folliculitis, eosinophilic folliculitis, rosacea, lichen planopilaris, and lupus erythematosus. Multiple biopsy specimens and a high index of clinical suspicion are required to make a definitive diagnosis. Well-established lesions show a dense perifollicular lymphocytic infiltrate with prominent folliculotropism (Figs. 59.5 and 59.6). The epidermis and interfollicular dermis are usually spared. However, minimal epidermotropism can be revealed in serial sections. Rare cases may also show various degree of syringotropism (Fig. 59.5). The infiltrate is composed mainly of atypical lymphocytes with cerebriform nuclei accompanied by plasma cells, eosinophils, and histiocytes. Follicular epithelium may contain variable amounts of mucin. There may be alteration of the follicle (Fig. 59.7), resulting in comedonal changes or keratin plugging. A granulomatous inflammation may sometimes be evident due to follicular rupture and destruction. Large cell transformation may be seen in some cases.

Immunohistochemistry and molecular studies: The immunophenotype is similar to that of classic MF, namely, CD3+ (Fig. 59.8), CD4+, and

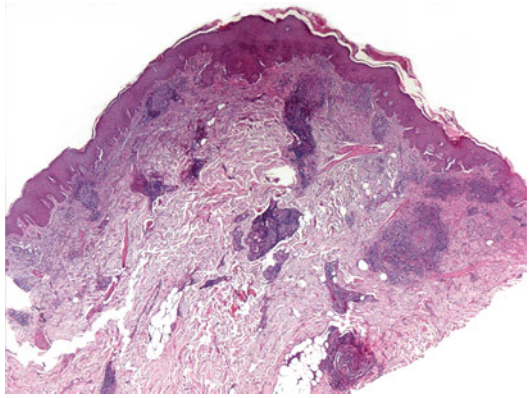

Fig. 59.5 Folliculotropic mycosis fungoides. This biopsy taken from a facial alopecic tumid plaque shows a striking adnexocentric infiltrate involving both follicular and eccrine epithelium without evident epidermotropism

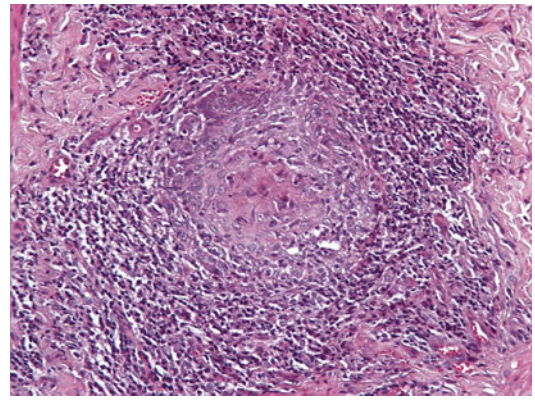

Fig. 59.6 Folliculotropic mycosis fungoides. There is a dense nodular perifollicular infiltrate with evident follicular epithelium involvement

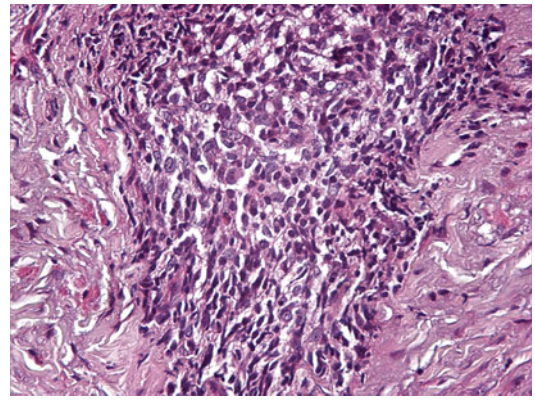

Fig. 59.7 Folliculotropic mycosis fungoides. The atypical lymphocytes with cerebriform nuclei invade and destroy the follicular epithelium

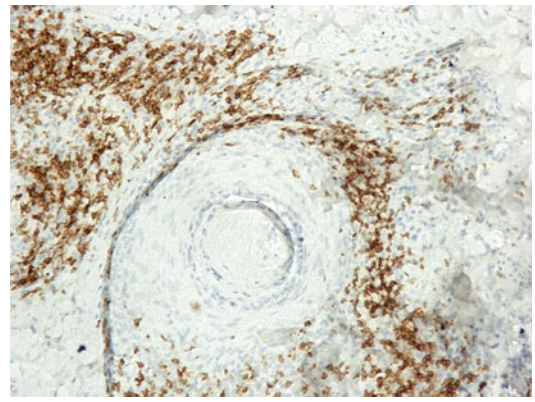

Fig. 59.8 Folliculotropic mycosis fungoides. The folliculotropic atypical lymphocytic infiltrate is positive for CD3

CD8–. There may be partial loss of CD7. The CD4:CD8 ratio is frequently 10:1 or greater, and the follicles characteristically show a high number of Langerhans (CD1a positive) cells. Molecular studies for TCR gamma gene rearrangement identify a monoclonal population, supporting the diagnosis of mycosis fungoides.

Differential Diagnosis

FMF must be distinguished from other benign or malignant conditions with follicular involvement such as folliculitis, eosinophilic folliculitis, pseudolymphomatous folliculitis, rosacea, lupus erythematosus, lichen planopilaris, and lymphomatoid papulosis. In folliculitis, the inflammatory cell infiltrate is more polymorphic without infiltrates of atypical lymphocytes. Pseudolymphomatous folliculitis is usually solitary and tends to resolve spontaneously. Eosinophilic folliculitis of both Ofuji disease and HIV-associated cases does not display atypical folliculotropic lymphocytes. Moreover, the clinical context is different. Early lesions of FMF may be easily confused with interface dermatitis like lupus erythematosus and lichen planopilaris. Attention to the distribution of the lymphocytic infiltrates (disposition at the dermoepidermal junction with dyskeratotic keratinocytes versus disposition in the follicular epithelium) coupled with a careful clinicopathologic correlation may aid in the differential diagnosis. Histopathologically, FMF may be very difficult to be distinguished from follicular lymphomatoid papulosis (LyP), especially of the type B. The differentiation is best achieved by close clinicopathologic correlation. LyP presents with crops of spontaneously regressing papules and nodules, whereas FMF improves only with treatment.

Prognosis

Compared to classic MF, FMF shows an aggressive course and a poor outcome, especially 10–15 years after the initial onset of disease.

Treatment

Early stage disease may benefit from skin-directed therapy such as PUVA therapy in association with retinoids, especially bexarotene, or interferon-alfa. However, the response to these therapies is not as good as with conventional MF. Patients with advanced disease may require aggressive therapies such as CHOP, liposomal doxorubicin, and gemcitabine. Alemtuzumab, total skin electron bean irradiation, and allogeneic stem cell transplantation have shown various rates of response.

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Rare Variants of Mycosis Fungoides: Granulomatous Slack Skin Variant of Mycosis Fungoides

60

Irina Margaritescu and A. Doru Chirita

Introduction

Granulomatous slack skin (GSS) represents an extremely rare variant of mycosis fungoides. The disease was first described in 1967 by Bazex, Dupre, and Christol under the designation "chalazodermic Besnier-Boeck-Schaumann's disease." In 1978, Ackerman renamed it "granulomatous slack skin." A decade later, Philip LeBoit and coworkers established the lymphomatous character of GSS by clonal rearrangement.

Clinical Features

GSS affects men more than women with a male-to-female ratio of 3:1. The age of onset ranges from 8 to 82 years, with a predominance for late childhood to mid-adult life. GSS typically involves intertriginous areas such as axillae and groins. However, it can also affect the flanks and lower abdomen, inner upper thighs, and arms, forearms, wrists, and hands. Other locations include the buttocks, lower back, upper back, and feet and calves. Rarely, the head and neck area, pelvis, and penile shaft may be involved. The lesions start as infiltrated erythematous patches and plaques, few centimeters in diameter. Some of them display a wrinkled atrophic surface, very reminiscent of those of parapsoriasis en plaques or poikiloderma atrophicans vasculare (Fig. 60.1). The lesions progressively enlarge to become bulky pendulous tumors, especially in intertriginous areas and flanks (Fig. 60.2). Cutis laxa-like changes and ulcerations may sometimes occur. Patients complain of fatigue, slight fever, night sweats, and pruritus. Lymphadenopathy, lymphedema, hepatosplenomegaly, generalized ichthyosis, and erythroderma are sometimes encountered. The time delay between the onset of the lesions and the diagnosis is variable. As it usually takes a few years until the patient develops the characteristic pendulous skin folds, the diagnosis is usually delayed. Clinically, GSS can be misdiagnoses as hidradenitis suppurativa, cutis laxa congenita and acquisita, and anetoderma.

Pathology

Skin biopsy reveals a patchy lichenoid and nodular infiltrate of lymphocytes extending from the superficial dermis to the subcutaneous fat and even to the skeletal muscle (Fig. 60.3). In the upper part of the dermis, the infiltrate composed of lymphocytes and histiocytes is somewhat

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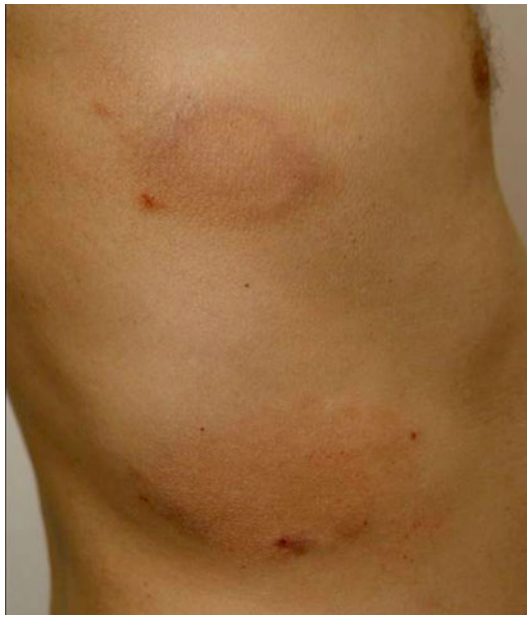

Fig. 60.1 Granulomatous slack skin variant of mycosis fungoides. Infiltrated erythematous plaques with a wrinkled atrophic surface reminiscent of those of parapsoriasis en plaques, on the right flank and intertriginous regions for 3 years

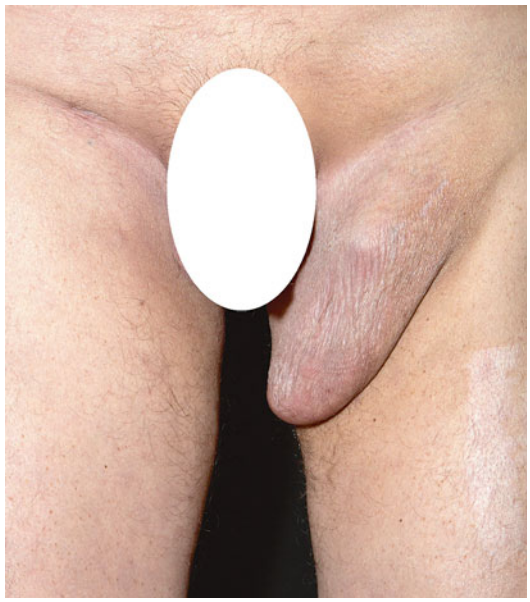

Fig. 60.2 Granulomatous slack skin variant of mycosis fungoides. The inguinal lesions progressively enlarged to become bulky pendulous tumors

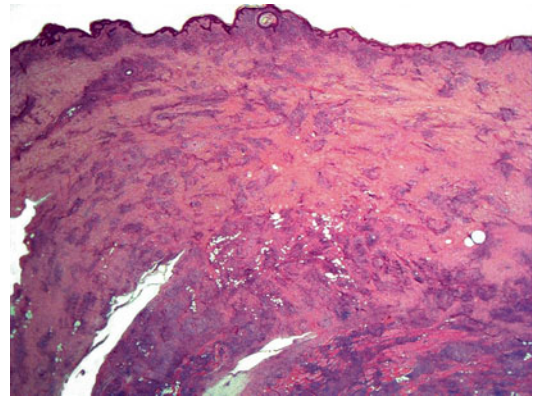

Fig. 60.3 Granulomatous slack skin variant of mycosis fungoides. Skin biopsy reveals a patchy lichenoid and nodular infiltrate of lymphocytes extending from the superficial dermis to the subcutaneous fat and skeletal muscle

band-like. The papillary dermis is thickened by haphazard fibrosis. The epidermis is usually uninvolved, but focal epidermotropism may sometimes be encountered. However, Pautrier microabscesses are absent. There is fibrosis and a mixture of lymphocytes and clustered histiocytes present throughout the dermis and extending into the subcutaneous fat and skeletal muscle. Some areas show extensive granulomatous infiltrate with an abundant number of granulomas. However, most of the areas are defined by a predominantly lymphocytic infiltrate which is secondarily joined by granulomatous inflammation. The dense infiltrate of lymphocytes is accompanied by countless, evenly spaced multinucleate histiocytes with extraordinary number of nuclei (Fig. 60.4). The giant cells are surrounded by a wreath-like arrangement of mononuclear cells and they also contain engulfed lymphocytes—lymphophagocytosis (Fig. 60.5). The lymphohistiocytic infiltrate is also accompanied by an increased number of eosinophils and plasma cells. The lymphocytes are not very atypical but some have enlarged and hyperchromatic, convoluted nuclei. Lymphocytes and giant cells are sometimes present into the walls of several medium and large vessels—granulomatous vasculitis (Fig. 60.6). Prominent elastolysis and

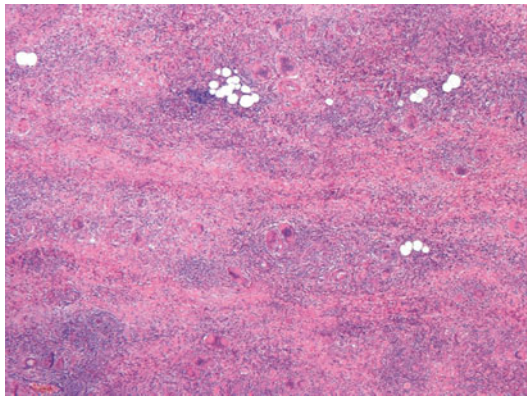

Fig. 60.4 Granulomatous slack skin variant of mycosis fungoides. The dense infiltrate of lymphocytes is accompanied by countless, evenly spaced multinucleate histiocytes with extraordinary number of nuclei

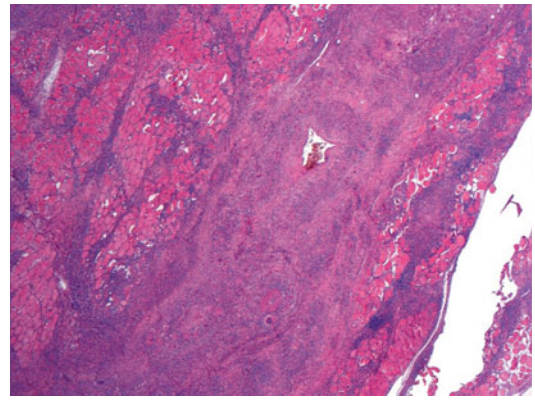

Fig. 60.6 Granulomatous slack skin variant of mycosis fungoides. Lymphocytes and giant cells are also present into the wall of a large vessel

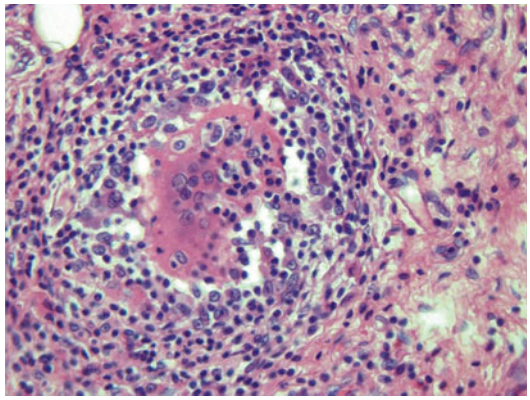

Fig. 60.5 Granulomatous slack skin variant of mycosis fungoides. The giant cells are surrounded by a wreath-like arrangement of mononuclear cells and they also contain engulfed lymphocytes—lymphophagocytosis

elastophagocytosis evidenced by an elastic van Gieson stain is a characteristic feature.

IHC and Molecular Studies: The lymphoid infiltrate displays a T-helper phenotype—CD2+, CD3+, CD4+, CD8−, and CD45RO+, sometimes with loss of CD5 and CD7 antigens. Few cases show a CD3+ CD4− CD8+ phenotype. CD30+ cells can sometimes be found. Histiocytes, including giant cells, express antigens associated with a monocyte-macrophage lineage such as CD14 and CD68, with minimal expression of dendritic markers CD1a and S-100. Monoclonal rearrangement of T-cell receptor genes can be demonstrated by polymerase chain reaction in most cases. Trisomy 8 has been reported in association with GSS in a few patients. Recently, genetic alterations with t(3;9)(q12;p24) have been reported in a case of GSS.

Differential Diagnosis

The differential diagnosis of GSS includes both nonneoplastic and neoplastic diseases. The granulomatous inflammation is sometimes very extensive so that GSS may be misdiagnosed as sarcoidosis, necrobiotic xanthogranuloma, or foreign-body reaction. Infectious diseases like leprosy and Rosai-Dorfman disease can also enter the differential. The presence of granulomatous vasculitis can make one think of other systemic processes like Wegener's granulomatosis. GSS should also be differentiated from other cutaneous lymphomas with granulomatous inflammation, mainly T-cell lymphomas but also B-cell lymphomas. The most important differential diagnosis is with MF with granulomatous inflammation (granulomatous MF). Compared with granulomatous MF, GSS is associated with a larger number of giant cells with a huge amount of nuclei, more prominent elastolysis and elastophagocytosis, and lack of evident epidermotropism and Pautrier microabscesses. Moreover, only

GSS is associated with hanging skin folds in intertriginous areas. Hodgkin lymphoma very rarely presents at extranodal sites. When cutaneous lesions appear in Hodgkin disease, almost always they represent secondary involvement.

Prognosis

GSS has a slowly progressive course with a 5-year survival rate of 100 %. However, the prognosis depends on the development of the second lymphoproliferative diseases, such as Hodgkin disease, other cutaneous T-cell lymphomas, acute myelogenous leukemia, and Langerhans cell histiocytosis. The second lymphoid neoplasia may precede, develop concomitantly, or follow the appearance of GSS. Hodgkin lymphoma is the most common second neoplasia in patients with GSS.

Treatment

There is no effective treatment for GSS even though many therapeutic modalities have been tried. These include skin-directed therapy (topical corticosteroids, topical chemotherapy with nitrogen mustard, PUVA therapy, radiotherapy, total skin electron beam therapy), systemic corticosteroids, interferon-alfa and interferon-gamma, retinoids, chemotherapy, and pentostatin. Surgical excisions of the pendulous skin folds are invariably followed by lesion reappearance.

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Rare Variants of Mycosis Fungoides: Localized Pagetoid Reticulosis (Woringer-Kolopp Type)

61

Irina Margaritescu and A. Doru Chirita

Introduction

Localized pagetoid reticulosis (LPR), originally described by Woringer and Kolopp in 1939, is a rare variant of mycosis fungoides (MF) with an indolent course, clinically characterized by a solitary hyperkeratotic plaque on the extremities and histopathologically by a markedly epidermotropic infiltrate of atypical T lymphocytes.

Clinical Features

LPR affects males more than women and has a wide age range at onset (range 2–79). It has a peculiar predilection for children (20 % of patients are <15 years old). LPR typically involves the distal extremities. It presents as solitary, slowly enlarging, persistent scaly erythematous patch or plaque with sharply demarcated borders measuring 0.7–30 cm in diameter (Fig. 61.1). The lesion is usually asymptomatic, but pruritus may sometimes be an accompanying feature. The lesion may mimic a wide range of both benign and malignant conditions such as psoriasis, nummular eczema, dermatophytosis, granuloma annulare, wart, necrobiosis lipoidica, elastosis perforans serpiginosa, Bowen's disease, and superficial basal cell carcinoma.

Pathology

Histologically, LPR demonstrates a hyperplastic epidermis with striking colonization by atypical lymphocytes, especially in the lower reaches (Fig. 61.2). The lymphocytes are distributed singly, in small clusters or in large lacunae (Fig. 61.3). Involvement of adnexal epithelium is often a feature. The lymphocytes are medium to large, with hyperchromatic irregular nuclei and abundant vacuolated cytoplasm (Fig. 61.4). They usually have a perinuclear halo. Mitotic figures are sometimes conspicuous. The papillary and superficial dermis shows a mixed cell infiltrate with very sparse atypical cells.

Immunohistochemistry and molecular studies: The atypical lymphocytes show expression of CD2, CD3, and CD5, with partial or total loss of CD7. Both T-helper (CD4+) and T-suppressor/cytotoxic (CD8+) phenotypes have been described. CD4/CD8 double-negative forms have also been reported. Loss of CD45RO (UCHL-1)

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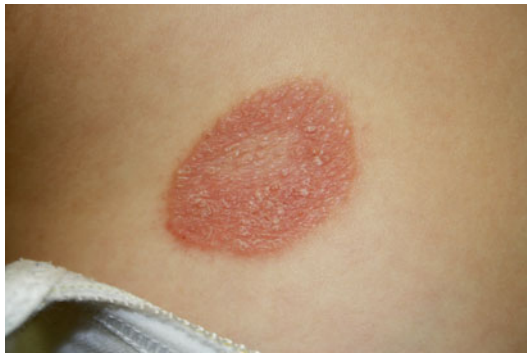

Fig. 61.1 Localized pagetoid reticulosis. A solitary, slowly enlarging, persistent erythematous patch with sharply demarcated borders for 10 years

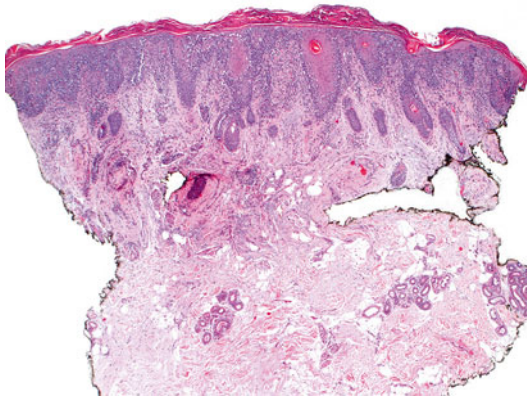

Fig. 61.2 Localized pagetoid reticulosis. This biopsy of an acral lesion shows an acanthotic psoriasiform epidermis covered by hyper-orto and parakeratosis and permeated by numerous lymphocytes

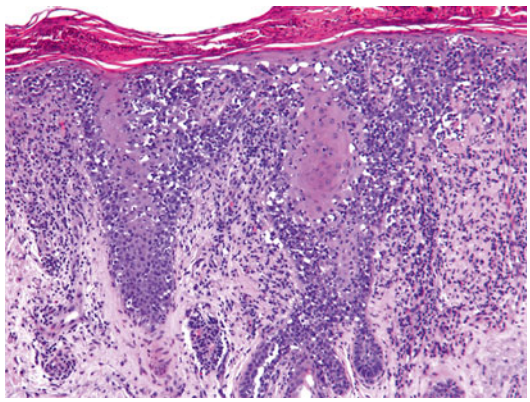

Fig. 61.3 Localized pagetoid reticulosis. The lymphocytes are disposed singly, in small clusters and in large lacunae at all levels of the epidermis, but especially in its lower reaches

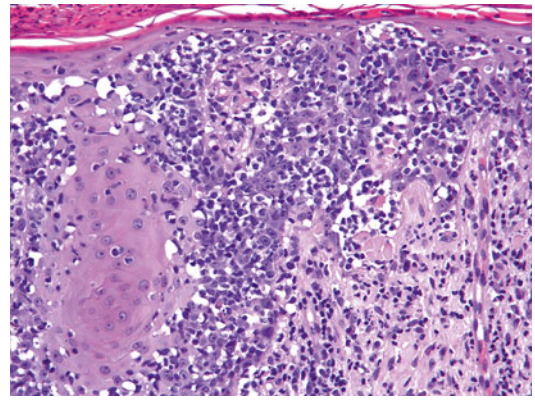

Fig. 61.4 Localized pagetoid reticulosis. The lymphocytes are medium to large with hyperchromatic, irregular, haloed nuclei

has been documented. Some cases may show high numbers of CD30+ cells. The atypical lymphocytes usually demonstrate a high proliferation rate (>30 %). Monoclonality of the infiltrate can be demonstrated by TCR gene rearrangements studies in most cases.

Differential Diagnosis

The main differential diagnoses include mycosis fungoides palmaris et plantaris, lymphomatoid papulosis, and CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma. Clinicopathologic correlation coupled with immunohistochemical studies aid in the distinction. LPR should also be distinguished from other entities with a pagetoid pattern of cell distribution such as melanoma, bowenoid squamous cell carcinoma, Paget's disease, Merkel cell carcinoma, and Langerhans cell histiocytosis.

Prognosis

LPR has an indolent behavior, with very slowly local extension. Resistances to therapy and local recurrence have rarely been reported.

Treatment

Surgical excision and radiotherapy represent the recommended treatment for LPR. Localized electron beam therapy is highly effective. Other treatment modalities such as potent topical steroids, topical nitrogen mustard, photochemotherapy, and narrowband UVB are other therapeutic options.

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Rare Variants of Mycosis Fungoides: Syringotropic Mycosis Fungoides

62

Irina Margaritescu and A. Doru Chirita

Introduction

The most recent WHO-EORTC classification lists syringotropic mycosis fungoides (SMF) as a distinct variant of MF that presents clinically as a solitary well-circumscribed alopecic red-brown plaque. Histologically, the plaque shows a heavy lymphoid infiltrate that surrounds and infiltrates the epithelium of the eccrine sweat glands and ducts. A propensity for eccrine glands and ducts involvement by the lymphoid infiltrate may also be encountered in conjunction with folliculotropic and conventional mycosis fungoides.

Clinical Features

SMF is seen most frequently in males in their fifth to sixth decade of life (age range 26–83). The most affected sites are the trunk and extremities, especially the areas that are usually involved by classic MF such as the flanks, abdomen, hips, breasts, buttocks, and groin. Palms and soles are also affected. Unlike follicular mycosis fungoides, lesions on the head and neck region are rarely encountered. SMF presents with solitary or more widespread lesions. The lesions are erythematous, hyperpigmented or hypopigmented, scaly patches, papules, or plaques (Fig. 62.1). Pruritus is usually an accompanying feature, but the lesions may also be hypoesthetic or even asymptomatic. Other associated features are anhidrosis and alopecia (Fig. 62.2). Occasionally, SMF presents with hyperkeratosis, palmoplantar keratoderma, nodules, lymphadenopathy, erythroderma, and Sezary syndrome.

Pathology

SMF is characterized by a dense lymphocytic infiltrate that surrounds and infiltrates the sweat gland and ductal epithelium (Fig. 62.3). The lymphocytes have characteristic hyperchromatic convoluted nuclei. The epithelium of the sweat glands and ducts shows various degrees of hyperplasia (Fig. 62.4) with luminal obliteration. Folliculotropism and epidermotropism are sometimes encountered.

Immunohistochemistry and Molecular Studies: The lymphocytes express CD2, CD3, CD4, and CD5, with partial or total loss of CD7. TCR gamma gene rearrangement studies may be used to identify monoclonality of the infiltrate.

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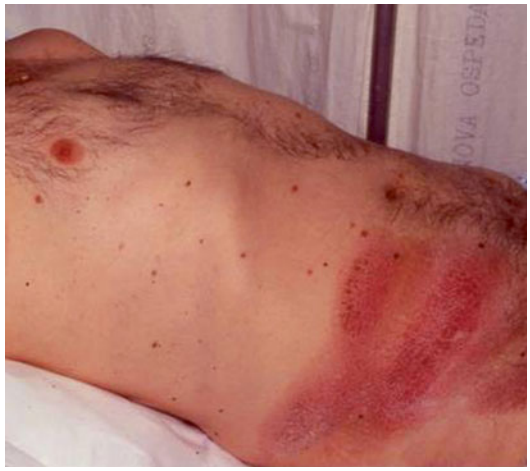

Fig. 62.1 Syringotropic mycosis fungoides. Erythematous, scaly patch with papules on the flank

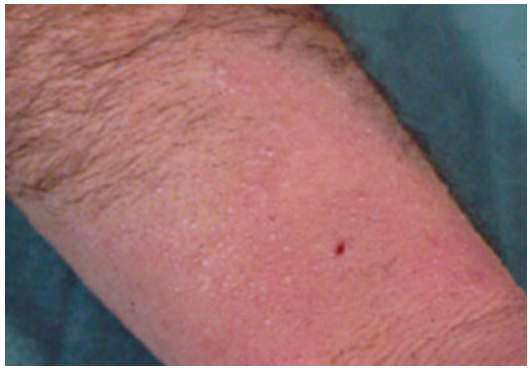

Fig. 62.2 Syringotropic mycosis fungoides. An alopecic patch with anhidrosis

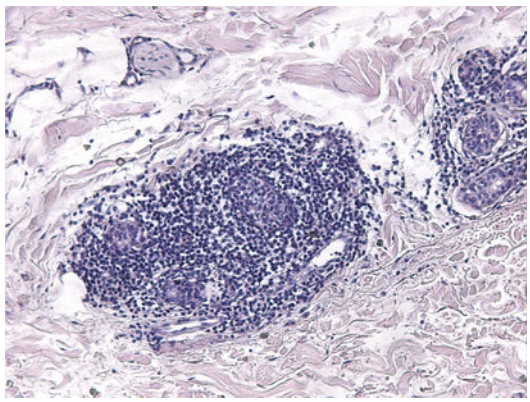

Fig. 62.3 Syringotropic mycosis fungoides. A dense lymphocytic infiltrate surrounds and infiltrates the sweat gland and ductal epithelium

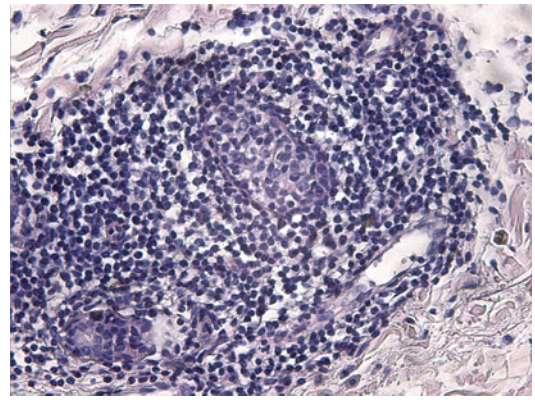

Fig. 62.4 Syringotropic mycosis fungoides. The atypical lymphocytes infiltrate the hyperplastic epithelium of the sweat glands with luminal obliteration

Differential Diagnosis

The histological differential diagnosis of SMF includes other conditions that involve eccrine ducts such as lymphoid drug eruption, lupus erythematosus, or lichen striatus. Clinicopathologic correlation and molecular studies, when needed, may be of help in establishing the correct diagnosis.

Prognosis

Definite conclusions regarding the prognosis of this variant of MF have been hindered by the small number of reported cases. From the studies published so far, it seems that SMF has a benign chronic course.

Treatment

Photochemotherapy, when used with a more aggressive photosensitization protocol, may be of benefit in treating localized SMF. However, local radiotherapy and extracorporeal photopheresis seem to be a more effective tool.

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Adult T-Cell Lymphoma/Leukemia

63

Werner Kempf and Marianne Tinguely

Introduction

Adult T-cell lymphoma/leukemia (ATLL) is a systemic T-cell non-Hodgkin lymphoma etiologically linked to human T-cell leukemia virus 1(HTLV-1). HTLV-1 infection and as a consequence ATLL is endemic in Japan, Central Africa, South America, and the Caribbean islands. Depending on the clinical presentation, an acute, a lymphomatous, a smoldering, and a chronic form of ATLL are distinguished. Peripheral blood involvement with leukemic spread can occur in acute and chronic form, but is not seen in the lymphomatous and smoldering variants. Regulatory T cells are regarded as the cell type which becomes transformed by HTLV-1 to initiate ATLL.

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Clinical Features

ATLL occurs in adults mostly in their fifth and sixth decade after a long latency of HTLV-1 infection, but may rarely occur in childhood. Men are more commonly affected than women (male/female ratio of 1.5:1). Skin involvement occurs in approximately 40–70 % of the patients during the disease course. The most prevalent form is acute ATLL manifesting with papules (Fig. 63.1), nodules (Fig. 63.2), tumors, or erythroderma, accompanied by leukemic spread, lymphoadenopathy, and hypercalcemia. In the chronic and smoldering forms, patches and plaques are found which clinically resemble mycosis fungoides (MF), but no or only low numbers of circulating tumor cells are found.

Pathology

In the acute and lymphomatous form, a superficial or diffuse dermal infiltrate of medium-sized to large pleomorphic cells with or without epidermotropism is found (Figs. 63.3 and 63.4). The findings resemble MF. In chronic or smoldering forms, often a subtle perivascular infiltrate with only a few atypical cells is present. The tumor cells exhibit a CD2+ CD4+ CD5+ CD8- CD25+ betaF1+ phenotype and may express CD30 but usually show downregulation of CD3 and lack CD7. In addition, expression of FOXP3 is

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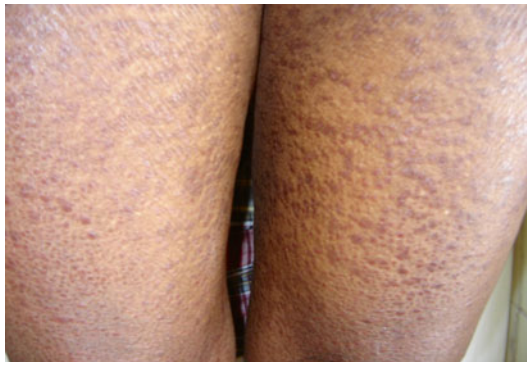

Fig. 63.1 ATLL, acute form: disseminated papules on both legs, nodules on the trunk and extremities (Courtesy of Dr. Dr Moussa Diallo, Dept. of Dermatology, University Hospital Dakar, Senegal)

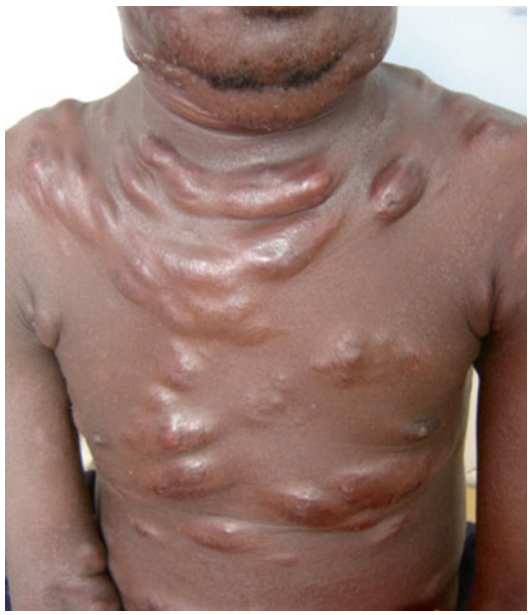

Fig. 63.2 ATLL, acute form: multiple tumors on the trunk (Courtesy of Dr. Dr Moussa Diallo, Dept. of Dermatology, University Hospital Dakar, Senegal)

typically found in ATLL. Monoclonal rearrangement of T-cell receptor genes and clonal integration of HTLV-1 into the host cell genome can be detected. In the peripheral blood, circulating tumor cells with convoluted nuclei are referred to as flower cells.

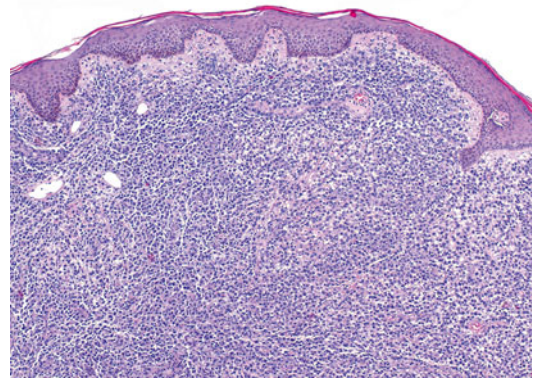

Fig. 63.3 ATLL, lymphomatous form: dense dermal infiltrates of atypical large lymphoid cells

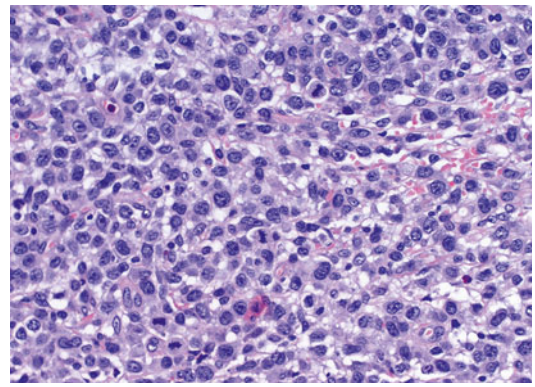

Fig. 63.4 ATLL, lymphomatous form: large tumor cells with pleomorphic nuclei and abundant cytoplasm

Differential Diagnosis

Due to overlapping clinical, histological, and immunophenotypic features, the most important differential diagnoses are MF, Sézary syndrome, cutaneous anaplastic large cell lymphoma, and cutaneous peripheral T-cell lymphoma, unspecified. They differ from ATLL by the absence of HTLV-1 infection.

Prognosis

Prognosis depends on the disease form with the acute and the lymphomatous forms exhibiting an aggressive course and poor prognosis

(median survival time of less than 1 year), whereas the smoldering and the chronic form are associated with a protracted course and median survival time of 2 years. Regarding skin involvement, ATLL manifesting with skin lesions, but without systemic involvement, shows better prognosis than patients with secondary skin involvement. Patients with patches and plaques have longer survival than cases with tumoral nodules or disseminated papules and erythroderma.

Treatment

Patients with chronic and smoldering forms are often not actively treated due to the rather indolent course. If treated, the combination of zidovudine and interferon-alfa is effective. For the aggressive forms of ATLL, first-line therapy includes multiagent chemotherapy or an antiviral combination of zidovudine and interferon-alfa. Alternatively, bexarotene, the proteasome inhibitor bortezomib, or the anti-CD52 antibody alemtuzumab has been employed. So far, durable remissions have only been achieved by allogeneic stem cell transplantation.

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Subcutaneous Panniculitis-Like T-Cell Lymphoma

64

Werner Kempf and Christina Mitteldorf

Introduction

SPTCL is a rare neoplasm accounting for 1 % of all cutaneous lymphoma, but it represents the most common form of lymphoma with subcutaneous involvement. SPTCL subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is defined by its primary subcutaneous localization and its phenotype with expression of the alpha/beta chain of the T-cell receptor (TCR). It differs phenotypically and prognostically from gamma/delta T-cell lymphoma (GD-TCL) often manifesting with predominantly subcutaneous tumorous infiltrates.

Clinical Features

The disease presents with erythematous, indurated, deep-seated skin infiltrates clinically mimicking erythema nodosum or other forms of panniculitis (Fig. 64.1). The legs are the predilection site. Ulceration may occur. Systemic signs may be present. In a subset of patients, SPTCL is complicated by the occurrence of hemophagocytic syndrome (HPS).

Pathology

SPTCL is characterized by lobular infiltrates composed of small- to medium-sized lymphoid cells with nuclear pleomorphism (Figs. 64.2 and 64.3). The rimming of adipocytes by tumor cells is a consistent feature, but is not disease-specific. Karyorrhexis and cytophagocytosis may be present. The tumor cells express CD3+ CD4- CD8+ CD56- phenotype and cytotoxic proteins such as TIA-1+, granzyme B+ and perforin (Fig. 64.4a) and show a high proliferative activity (Fig. 64.4b). By definition, expression of TCR alpha/beta has to be demonstrated by immunohistochemistry (betaF1). There is no association with Epstein-Barr virus (EBV). Clonal rearrangement of the alpha/beta chain of the T-cell receptor is found.

Differential Diagnosis

SPTCL has to be distinguished from subcutaneous form of GD-TCL, which shows overlapping histological features with predominantly lobular infiltrates of atypical lymphocytes of varying size. In contrast to SPTCL, GD-TCL exhibits expression of TCR gamma/delta (TCR gamma+ or TCR delta+) and in most cases CD56. Extranodal T/NK-cell lymphoma, nasal type, can be differentiated by the expression of CD56

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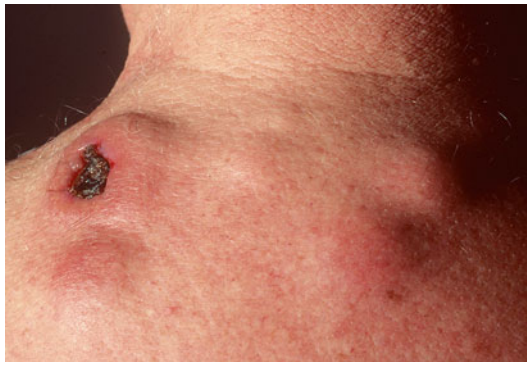

Fig. 64.1 SPTCL: Infiltrated deep-seated skin lesions on the neck with ulceration (Courtesy of Prof. Dr. G. Burg, Zürich)

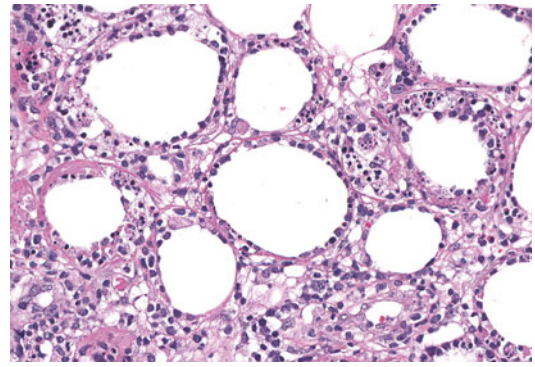

Fig. 64.3 SPTCL: The adipocytes are surrounded by neoplastic lymphocytes with moderately chromatin dense nuclei (so-called rimming)

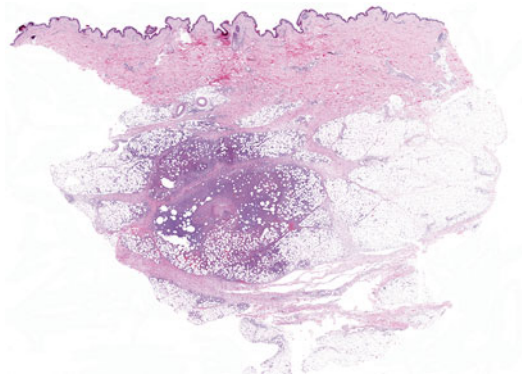

Fig. 64.2 SPTCL: Lobular infiltrates in the subcutis (Note absence of infiltrates in the dermis)

and EBV. Lupus panniculitis lacks significant atypia of lymphocytes and shows often lymphoid follicles with reactive germinal centers and clusters of CD123+ plasmacytoid dendritic cells. In individual cases, however, differentiation between lupus panniculitis and SPTCL may be very challenging, especially since occurrence of both disorders has been observed in the same individuals. Rarely, subcutaneous infiltrates in the context of *Borrelia* infection can mimic SPTCL. The relationship of SPTCL to cytophagic histiocytic panniculitis (CHP) remains to be clarified, especially since some cases of CHP may represent SPTCL.

Prognosis

SPTCL has a favorable prognosis with a 5-year survival rate of 80 %, which contrasts with the poor prognosis of subcutaneous GD-TCL. The course is indolent and slowly progressive in most patients. Tumor spread to other tissues is rare. HPS however is associated with mortality.

Treatment

A "wait-and-see" strategy may be justified in some patients with only limited number of lesions. Active treatment includes systemic steroids and low-dose methotrexate.

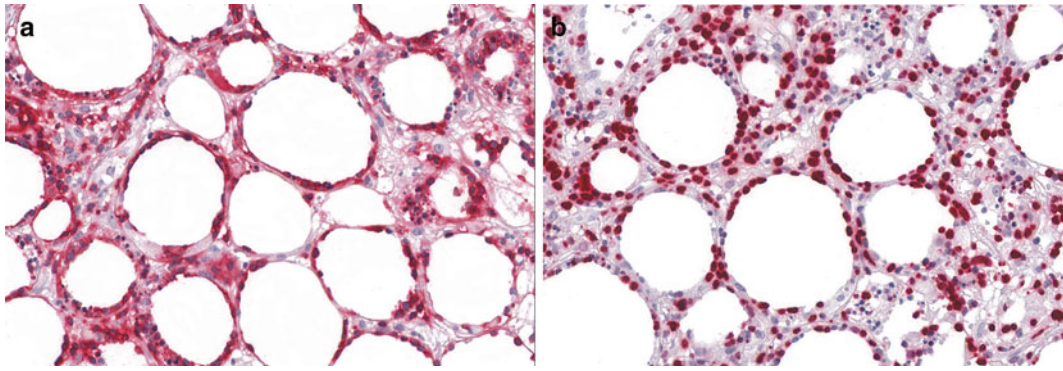

Fig. 64.4 SPTCL: Expression of CD8 (**a**) and high proliferative activity (Ki67) (**b**) by the tumor cells

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Extranodal NK/T-Cell Lymphoma: Nasal Type

65

Werner Kempf and Christina Mitteldorf

Introduction

Extranodal NK/T-cell lymphoma (ENTL), nasal type, is a rare and aggressive lymphoma with an angioinvasive growth, a cytotoxic phenotype, and an association with Epstein-Barr virus (EBV). The nasal cavity and paranasal areas are most commonly involved, but the disease spreads to the skin, gastrointestinal tract, testis, or lymph nodes. The skin represents the second most common site of involvement.

Clinical Features

In the skin, ENTL manifests with papules or ulcerated nodules (Fig. 65.1). Systemic symptoms are common and include fever, malaise, and weight loss. ENTL may be complicated by hemophagocytic syndrome. ENKTL affects more commonly men. Hydroa vacciniforme-like lymphoma represents a rare and aggressive variant of ENTL mostly occurring in the Central and South America. It affects young adults and children and presents with facial edema and disease progression to blisters, ulcers, and scarring on sun-exposed areas.

Pathology

ENTL is characterized by dense dermal and subcutaneous infiltrates with an angiocentric and angiodestructive growth resulting in necroses and ulceration (Figs. 65.2 and 65.3). The tumor cells are of variable size ranging from small to large cells with pleomorphic nuclei and pale cytoplasm (Fig. 65.3). Mitoses are common. In some cases, numerous admixed reactive cells such as eosinophils, plasma cells, and histiocytes are observed. The tumor cells express CD2, cytoplasmic CD3 (CD3e), CD56, as well as cytotoxic proteins (T1A-1, granzyme B, and perforin). Presence of EBV in the neoplastic cells can be demonstrated by in situ hybridization in nearly all cases of secondary cutaneous NK/T- and NK-cell lymphomas (Fig. 65.4) but is reported to be rarely found in primary cutaneous forms of ENTL. Most cases are in germline configuration, but clonal T-cell receptor gene rearrangement can be detected in a minority of the cases.

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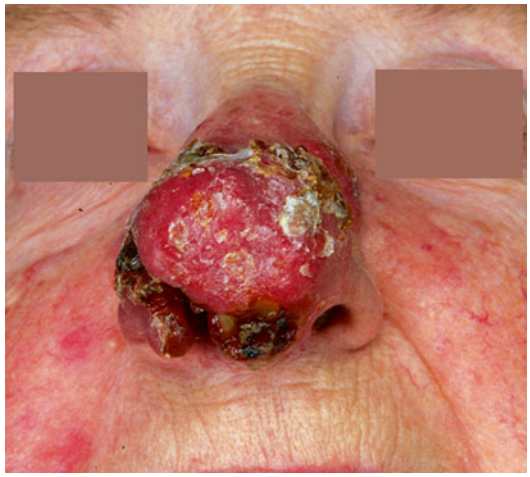

Fig. 65.1 ENTL, nasal type: Ulcerated tumor in the nasal area (Courtesy of Dr. Alistair Robson, London, UK)

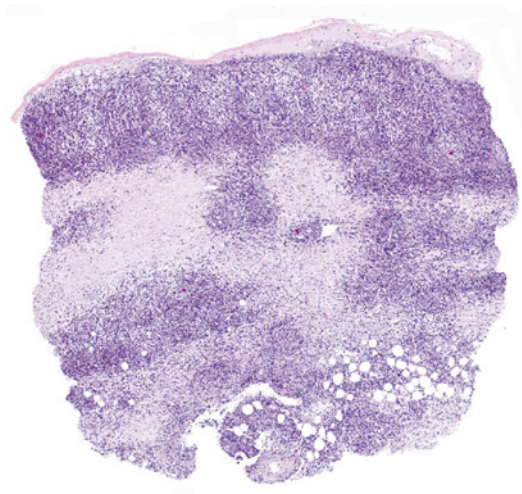

Fig. 65.2 ENTL, nasal type: Dermal and subcutaneous infiltrates

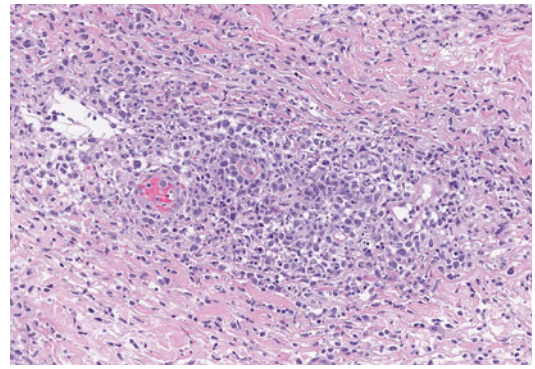

Fig. 65.3 ENTL, nasal type: Angiocentric and angiodestructive infiltrates of medium-sized to large tumor cells with pleomorphic nuclei

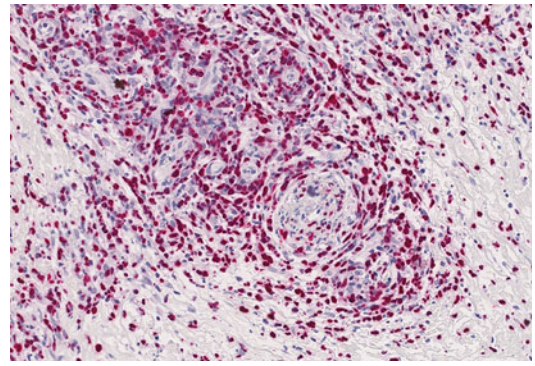

Fig. 65.4 ENTL, nasal type: Detection of EBV in all tumor cells by in situ hybridization

Differential Diagnosis

Differential diagnosis includes other CD56+ and/or EBV-associated T- or NK-cell lymphomas as well as lymphomas with angioinvasive growth pattern including cutaneous gamma/delta T-cell lymphoma, pagetoid reticulosis, subcutaneous panniculitis-like T-cell lymphoma, and primary cutaneous or secondary cutaneous peripheral T-cell lymphoma, unspecified. Immunophenotyping and especially detection of EBV are useful to distinguish ENTL from the abovementioned lymphomas. EBV-associated mucocutaneous ulcer is a B-cell lymphoproliferation often arising in the context of drug-related immunosuppression which differs by the morphology and B-cell phenotype of the atypical lymphoid cells resembling Reed-Sternberg or Hodgkin-like cells and the excellent prognosis after withdrawal of underlying immunosuppression.

Prognosis

Prognosis is intermediate to poor with survival rates between 30 % and 60 %. The median survival time is 12–15 months. EBV DNA copy

numbers are associated with tumor burden and are a predictive prognostic factor. Remarkably, cases with an unusual protracted course recently were reported.

Treatment

Chemoradiotherapy or L-asparaginase-based regimens including SMILE (steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide) improved survival of ENTL patients. Hematopoietic stem cell transplantation may represent a promising therapeutic approach.

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Primary Cutaneous CD8+ Aggressive Epidermotropic Cytotoxic T-Cell Lymphoma

66

Werner Kempf and Alistair Robson

Introduction

CD8+ AECTCL is a very rare but highly aggressive neoplasm of CD8+ cytotoxic T cells. Fewer than 100 cases have been documented, mostly as case reports or small case series. Most patients are affected in the fifth to seventh decade.

In the WHO classification (4th edition, 2008) primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (CD8+ AECTCL) is listed as a provisional entity among the rare subtypes of cutaneous peripheral T-cell lymphomas. The designation "Berti lymphoma" refers to the first description by E. Berti in 1999.

Clinical Features

This lymphoma manifests with rapidly evolving disseminated erosive patches, plaques, or necrotic and ulcerated, hemorrhagic papules and nodules (Fig. 66.1). In some patients, hyperkeratotic patches and plaques and annular lesions may be observed. Spread to extracutaneous sites, particularly the oral mucosa, visceral organs (lung), and central nervous system, often occurs, whereas the lymph nodes are usually not involved.

Pathology

Histology shows prominent epidermotropism of mostly small to medium atypical lymphocytes with chromatin dense nuclei (Figs. 66.2 and 66.3). Apoptotic keratinocytes and spongiosis are commonly found, and blister formation may occasionally be seen. Extension of the lymphocytic infiltrates into the deeper dermis and subcutis with angiocentric growth and destruction of adnexal structures can occur. Hemorrhage is common.

The tumor cells express CD3, CD8 (Fig. 66.4), and CD45RA, betaF1, as well as TIA-1 and other cytotoxic proteins, but are negative for CD4, CD30, CD56, CD45RO, and often CD5. The proliferative index (Ki-67) is high (>50 %). A CD2–CD7+ phenotype seems to be associated with a more aggressive course. A clonal rearrangement of T-cell receptor genes can be demonstrated in most cases. There is no association with Epstein–Barr virus.

Differential Diagnosis

The differential diagnosis is broad and includes CD8+ mycosis fungoides (MF) which also displays an epidermotropic infiltrate, but only few

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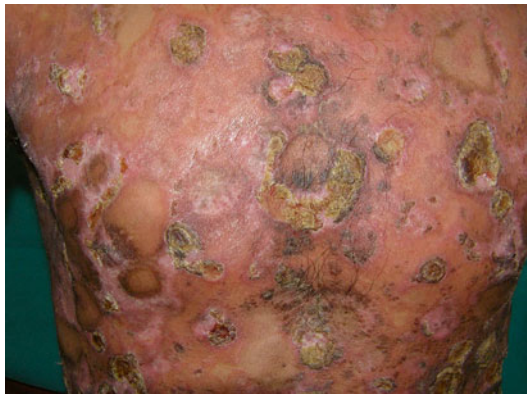

Fig. 66.1 CD8+ AECTCL: Clinical presentation with disseminated erosive plaques on the trunk (By courtesy of Dr. Dipendra Gurung, Kathmandu, Nepal)

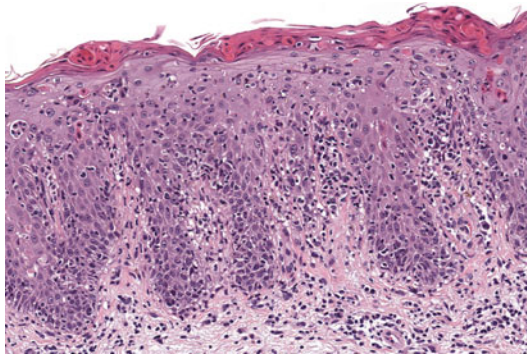

Fig. 66.2 CD8+ AECTCL: Superficial band-like infiltrate with epidermotropism and ulceration

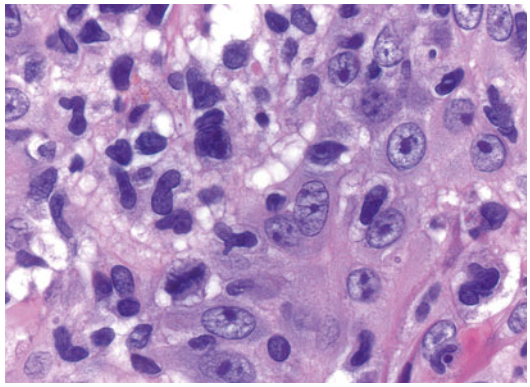

Fig. 66.3 CD8+ AECTCL: Epidermotropic infiltrate of small- to medium-sized lymphocytes with convoluted nuclei (Note apoptotic keratinocytes)

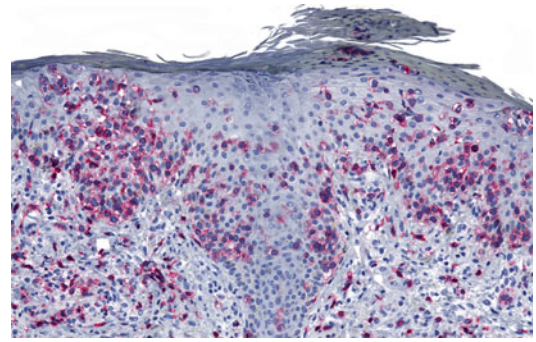

Fig. 66.4 CD8+ AECTCL: Characteristic expression of CD8 by tumor cells

or no necrotic keratinocytes are found and epidermal necrosis is absent. More importantly, CD8+ MF clinically differs from CD8+ AECTCL by hyper- or hypopigmented patches and plaques lacking erosions or ulceration. Pagetoid reticulosis is an indolent unilesional MF subtype displaying prominent epidermotropism and various phenotypes including expression of CD8. The clinical presentation, however, with a solitary lesion allows clear-cut distinction from CD8+ AECTCL. Lymphomatoid papulosis type D showing epidermotropic infiltrates of small- to medium-sized CD8+ CD30+ lymphocytes differs from CD8+ AECTCL by the typical clinical presentation with self-regressing and recurrent papules and small nodules. Pityriasis lichenoides et varioliformis acuta (PLEVA) represents a histological differential diagnosis, especially when expressing CD8+ and due to the presence of necrotic keratinocytes, but it clinically shows scaly maculopapular lesions and histologically lacks significant nuclear atypia of the lymphocytes.

Prognosis

CD8+ AECTCL shows an aggressive course with a median survival of fewer than 32 months and a 5-year survival rate of only 18 %. Only a small subset of patients appears to have a less aggressive course.

Treatment

Multiagent chemotherapy may be initially effective, but is followed by rapid relapse. Combination of chemotherapy and autologous stem cell transplantation may represent a promising therapeutic approach.

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Primary Cutaneous γ/δ T-Cell Lymphoma

67

Werner Kempf

Introduction

γ/δ+ T-cell lymphomas represent clonal proliferations of mature-activated γ/δ T cells and comprise hepatosplenic and primary cutaneous forms. Cutaneous γ/δ+ T-cell lymphomas (CGD-TCL) is a rare but aggressive lymphoma. γ/δ T cells belong to the innate immunity and represent a small subset (<5 %) of all lymphocytes in the peripheral blood. They express the γ/δ T-cell receptor and cytotoxic molecules. Upon activation γ/δ T cells express one or more natural killer (NK)-associated surface molecules (CD56, CD16, CD57).

Clinical Features

CGD-TCL manifests with necrotic or ulcerated papules, plaques or nodules, and B symptoms (Fig. 67.1). The oral mucosa is commonly involved, whereas lymph nodes, spleen, and bone marrow are usually spared. Especially in the subcutaneous form, GD-TCL can be complicated by a hemophagocytic syndrome, which is defined by fever, splenomegaly, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, elevated serum ferritin, as well as evidence of hemophagocytic histiocytosis in the bone marrow, spleen, or lymph nodes.

Pathology

CGD-TCL shows epidermotropic, dermal (diffuse or nodular), and/or subcutaneous infiltrates. The subcutaneous form displays predominantly lobular infiltrates (Fig. 67.2). The neoplastic cells are of variable size, mostly medium-sized to large with irregular chromatin-dense or vesicular nuclei (Fig. 67.3). Angioinvasive growth and necrosis are common features. CGD-TCL displays a CD2+ CD3+ CD56+ phenotype with expression of cytotoxic molecules (TIA-1, granzyme B, perforin) (Fig. 67.4). The tumor cells are often CD4/CD8 double negative. By definition, the neoplastic cells express TCR γ/δ and lack TCR α/β (βF1). The γ/δ+ TCR phenotype can be demonstrated by expression of TCR delta-1 (TCRδ+) on fresh-frozen tissue or TCR gamma (TCRγ+) on formalin-fixed, paraffin-embedded sections. Molecular studies reveal clonal rearrangement of TCR gamma or delta genes. The presence of isochromosome 7q is a common genetic abnormality. EBV is generally negative.

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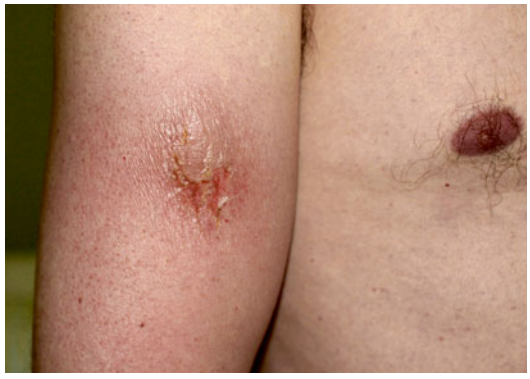

Fig. 67.1 Subcutaneous GD-TCL: Infiltrated and ulcerated plaque on the arm (By courtesy of Dr. B. Pfeiff, Germany)

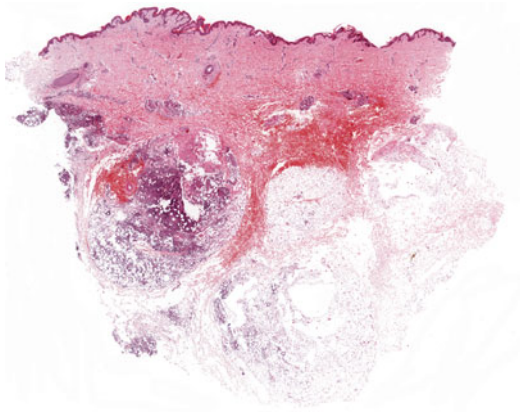

Fig. 67.2 Subcutaneous GD-TCL: Predominantly subcutaneous lobular infiltrates

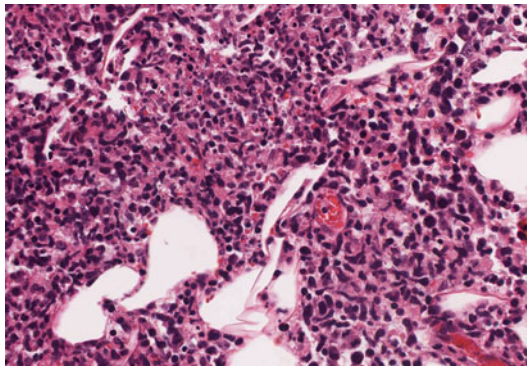

Fig. 67.3 Subcutaneous GD-TCL: Infiltrates of small- to medium-sized lymphocytes with atypical chromatin-dense nuclei

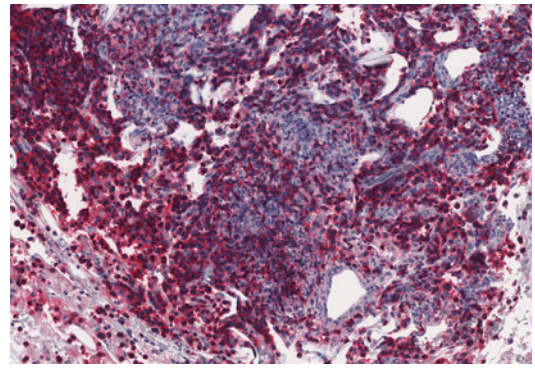

Fig. 67.4 Subcutaneous GD-TCL: Expression of CD56 by tumor cells

Differential Diagnosis

Histologically epidermotropic forms of CGD-TCL simulate mycosis fungoides (MF) and its subtype pagetoid reticulosis (PR), which may occasionally express a γ/δ+ TCR phenotype, but otherwise show classic clinical and histological features of MF (non-erosive patches and plaques) and PR (solitary plaque), respectively, and have an indolent course. The subcutaneous form of GD-TCL has to be distinguished from subcutaneous panniculitis-like T-cell lymphoma, which is defined by the expression of a TCR α/β+ phenotype as the main discriminating feature. The latter shows a favorable prognosis which contrasts to the aggressive course of GD-TCL. Further differential diagnosis of subcutaneous GD-TCL includes extranodal NK/T-cell lymphoma, nasal type, which is associated with EBV and displays a CD3ε+ CD56+ phenotype.

Prognosis

CGD-TCL runs an aggressive course with a median survival of 15 months and a 5-year survival rate of 33 %.

Treatment

CGD-TCL responds poorly to multiagent chemotherapy. Hematopoietic stem cells transplantation may provide a promising therapeutic strategy.

Sporadic observations reported patients with a less aggressive form of the disease, which can be controlled by UV light treatment in combination with steroids, retinoids, or methotrexate.

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Diffuse Large B-cell Lymphoma: Leg Type

68

Werner Kempf and Christina Mitteldorf

Introduction

DLBL-LT represents the most common type of diffuse large B-cell lymphoma arising in the skin. It is characterized by its growth pattern, the cytomorphology, and its immunophenotype. In contrast to the low-malignant indolent primary cutaneous follicle center lymphoma (PCFCL) and the primary cutaneous marginal zone lymphoma, DLBL-LT has a poor prognosis.

Clinical Features

DLBL-LT affects mostly elderly patients in their seventh and eight decade and occurs much more commonly in women (male to female ratio 1:3–4). In the majority of the patients, DLBL-LT manifests with solitary or multiple rapidly growing nodules located on the legs, particularly on the lower legs (Fig. 68.1), but lesions may develop also at other body regions such as the trunk. The tumors tend to ulcerate.

Pathology

A dense diffuse dermal infiltrate of centroblast- and immunoblast-like cells with non-cleaved, i.e., round nuclei and mitotic activity, is found (Figs. 68.2 and 68.3). There are only a few admixed small lymphocytes or other reactive cells. Rarely, epidermotropic, angiocentric, anaplastic, and spindle cell variants are observed. The tumor cells in DLBL-LT strongly express bcl-2 and MUM-1 as well as IgM, but show weak or no expression of bcl-6 and CD10. Networks of CD21-positive follicular dendritic cells are absent. Deletions in 9p21 (p14(ARF)/p16(INK4a)CDKN2A) are a common finding in DLBL-LT. There is no association with Epstein-Barr virus (EBV).

Differential Diagnosis

The prognostically most relevant differential diagnosis of DLBL-LT is PCFCL with a diffuse growth pattern. The distinction is based on cytomorphology (centrocyte-like in PCFCL vs. centroblast- and immunoblast-like differentiated tumor cells in DLBL-LT) as well as the phenotype with expression of bcl-2, MUM-1, and FOXP1 in DLBL-LT (Fig. 68.4). Secondary cutaneous involvement by nodal DLBL requires

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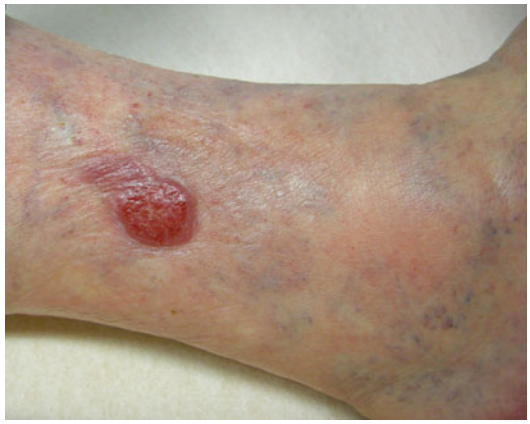

Fig. 68.1 DLBL-LT: Solitary nodule on the lower leg

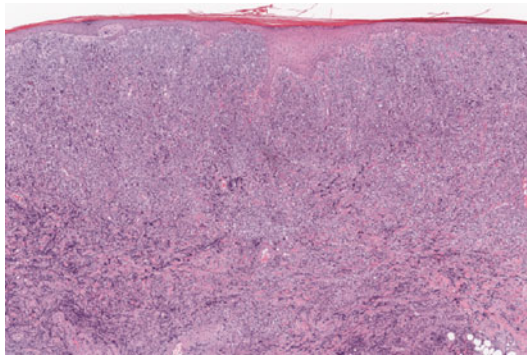

Fig. 68.2 DLBL-LT: Diffuse dermal infiltrate of blasts

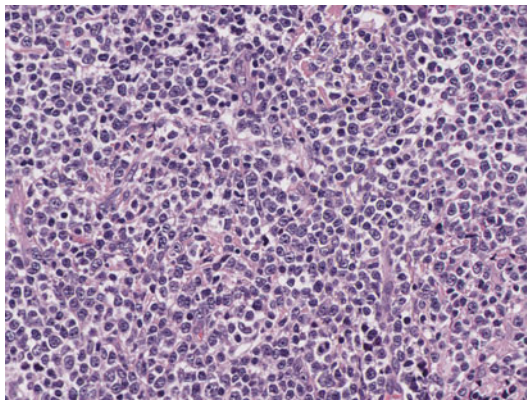

Fig. 68.3 DLBL-LT: Centroblast- and immunoblast-like differentiated tumor cells

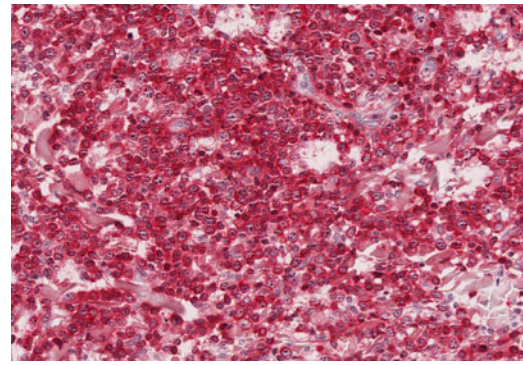

Fig. 68.4 DLBL-LT: Characteristic strong expression of bcl-2 by the tumor cells

staging. Other blastic neoplasias such as Merkel cell carcinoma, mantle cell lymphoma, or EBV-associated DLBL of the elderly are distinguished by their phenotypic profile and/or EBV status.

Prognosis

DLBL-LT carries a poor prognosis with a 5-year survival rate ranging from 20 % to 60 %. Factors indicating a poor prognosis include the presence of multiple tumoral lesions, involvement of both legs, chromosomal loss of 9p21, and activation of NFkB pathway with inhibition of antiapoptotic proteins.

Treatment

DLBL-LT requires treatment with chemotherapy in combination with rituximab, particularly in patients with multiple tumors. Solitary lesions may be treated by surgical excision and/or radiation.

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Intravascular Lymphoma

69

Werner Kempf and Christina Mitteldorf

Introduction

Intravascular lymphoma (IVL) is a rare lymphoma which is characterized by intravascular growth of large B cells especially in small vessels such as capillaries and venules. The B-cell form is much more common than the very rare T- or NK-cell form of IVL. A systemic and a cutaneous form of IVL can be distinguished.

Clinical Features

In the skin, IVL manifests with nodules, which may show ulceration, and livedo-like reticular erythema, panniculitis-like lesions, or painful telangiectasias simulating inflammatory skin diseases. Intravascular large B-cell lymphoma (IVBL) affects mostly patients in their sixth decade but has also been observed in children. In the systemic form of IVL, B symptoms (fever, night sweat, weight loss) are found in about half of the patients, and neurologic deficits can occur. IVL can be complicated by hemophagocytic syndrome.

Pathology

In the skin, small dermal and subcutaneous vessels are filled with large lymphoid cells with pleomorphic, moderately chromatin-dense nuclei, and abundant cytoplasm (Figs. 69.1 and 69.2). Colonization of hemangiomas by tumor cells was documented. In IVBL, the tumor cells express CD20 as well as bcl-2 and may be positive for CD5 and/or CD10 (Fig. 69.3). In the rare T-cell and NK-cell variant of intravascular lymphomas, T- or NK-cell markers such as CD3 and CD56 as well as cytotoxic markers are expressed by the tumor cells. Some cases of T- or NK-cell IVL are associated with Epstein-Barr virus. Alterations in homing receptors with lack of CD29 (beta1 integrin) and CD54 (ICAM-1) adhesion molecules on tumor cells have been identified and may play a role in the peculiar intravascular accumulation of tumor cells and the pathogenesis of IVBL.

Differential Diagnosis

The diagnosis is based on the characteristic intravascular growth and the phenotype of the tumor cells. Among lymphomas, intravascular CD30+

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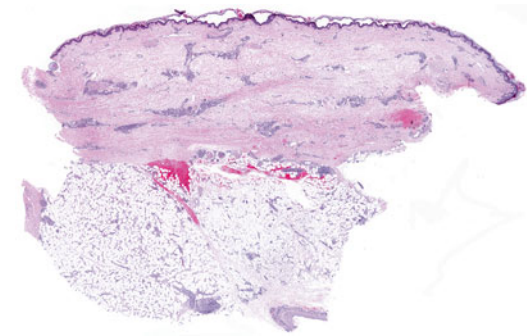

Fig. 69.1 IVBL: Dermal and subcutaneous vessels appear prominent in the scanning magnification

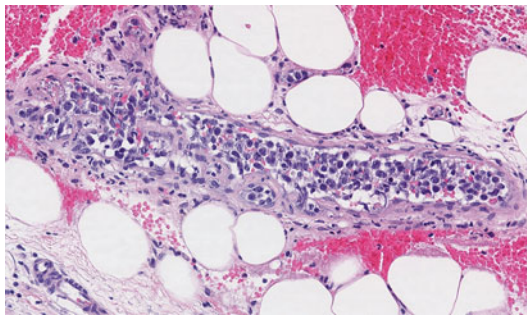

Fig. 69.2 IVBL: Subcutaneous vessel filled by large atypical lymphoid cells with nuclear pleomorphism

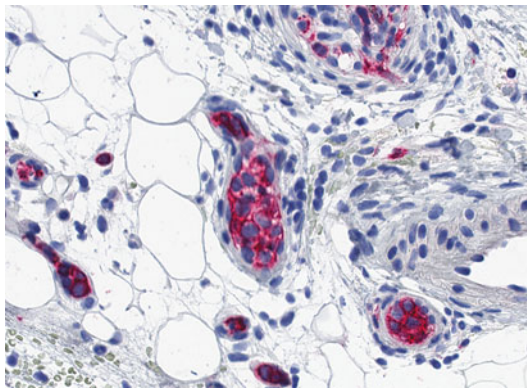

Fig. 69.3 IVBL: The intravascular tumor cells express the B-cell marker CD20

anaplastic large T-cell lymphoma is distinguished by the phenotype of tumor cells. Benign atypical intravascular CD30+ T-cell proliferation due to trauma or inflammation represents a reactive condition mimicking intravascular lymphoma. Differential diagnosis also includes leukemia and intralymphatic histiocytosis as it can be seen after orthopedic metal implantation or in patients with rheumatoid arthritis.

Prognosis

IVBL carries an unfavorable prognosis. The cutaneous form displays however a better prognosis with 3-year survival rate of 56 % compared to the systemic form of IVBL (33 %).

Treatment

IVBL is treated with multiagent chemotherapy, which seems, however, not to be very effective.

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Blastic Plasmacytoid Dendritic Cell Neoplasm

70

Werner Kempf

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare neoplasm of plasmacytoid dendritic cells (PDC) which very often affects the skin and shows a leukemic phase in the majority of the patients.

Clinical Features

In the skin, BPDCN presents with nodules or contusiform, bruise-like disseminated patches mostly on the trunk and head (Fig. 70.1). Oral mucosal involvement is commonly found. At the time of diagnosis or shortly after, leukemic spread with circulating malignant cells and bone marrow involvement occurs in 70 % of the patients. The central nervous system may become involved, whereas spread to lymph nodes is rare. In some patients, BPDCN develops in the context of preceding myelodysplastic syndrome.

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Pathology

In fully developed skin lesions, there is a dense dermal monomorphous infiltrate of blasts. The infiltrate is separated from the epidermis by a grenz zone (Fig. 70.2). The blastic tumor cells display nuclei with fine-dispersed chromatin and a sparse cytoplasm (Fig. 70.3). Extravasated erythrocytes are a characteristic finding which leads to the contusiform clinical aspect of the skin lesions. In early lesions, only subtle perivascular infiltrates composed of smaller blasts, lymphocytes, and histiocytes may be present (Fig. 70.4).

The tumor cells display a characteristic phenotype with expression of CD4, CD56, CD123, CD303, and TCL-1. Apart from CD123, expression of additional PDC markers such as BDCA-2, BCL11a, and CD2AP can be demonstrated. There is variable expression of TdT. Incomplete phenotypes with loss of markers have been observed. There is no reactivity for B- and T-cell markers except for very rare cases expressing CD3. T-cell receptor genes and immunoglobulin genes are not rearranged. The 9p21.3 (CDKN2A/CDKN2B), 13q13.1-q14.3 (RB1), 12p13.2-p13.1 (CDKN1B), 13q11-q12 (LATS2), and 7p12.2 (IKZF1) regions are commonly deleted in BPDCN.

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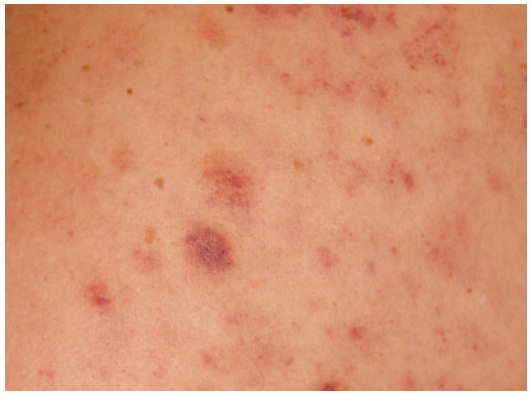

Fig. 70.1 BPDCN: Clinical manifestation with contusiform macules on the trunk

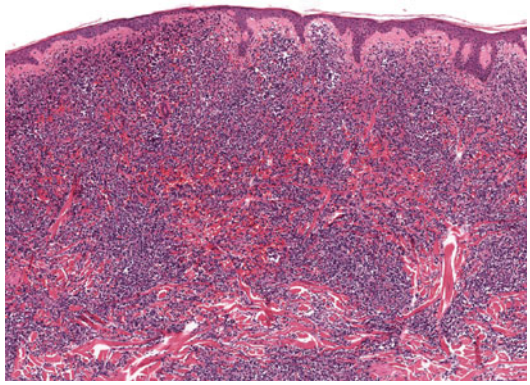

Fig. 70.2 BPDCN: Dense dermal infiltrates of blasts

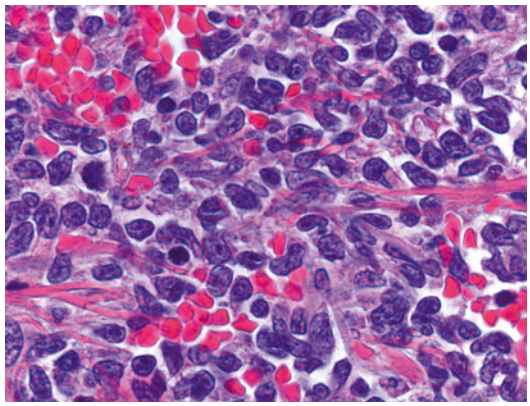

Fig. 70.3 Blasts representing neoplastic Plasmacytoid dendritic cells. Note the extravasated erythrocytes

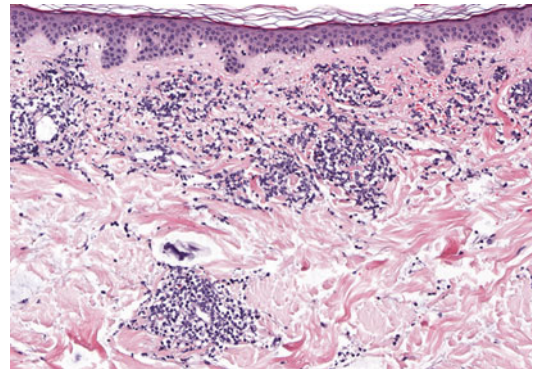

Fig. 70.4 BPDCN: Superficial perivascular infiltrates of blasts, lymphocytes, and histiocytes in a patient with leukemic spread

Differential Diagnosis

Acute and chronic myeloid and myelomonocytic leukemia (AML/AMML/CML) show overlapping clinical, histological, and phenotypic features, but TCL-1 is not expressed by tumor cells in AML/AMML, and extravasated erythrocytes are not a typical finding of specific skin infiltrates of AML/AMML. Large B-cell lymphomas and neuroendocrine carcinomas can be distinguished by their phenotypic profile. Reactive accumulations of PDC may occur in the context of AML and may mimic BPDCN.

Prognosis

BPDCN exhibits a poor prognosis with an aggressive course and a median survival of 12 months to 2 years despite initial response to treatment. CD303 expression and high proliferative index (Ki-67) were significantly associated with longer survival. Age over 40 years and biallelic loss of locus 9p21.3 indicate a shorter survival.

Treatment

Multiagent chemotherapy and allogeneic bone marrow transplantation are the first-line treatment and may in some patients result in long-term survival.

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Part XIII

Cutaneous Metastases of Internal Malignancies

Cutaneous Metastases of Breast Carcinoma

71

Irina Margaritescu

Introduction

Breast cancer is very common in women, accounting for 30 % of all cancers. Breast cancer in men accounts for only 1 % of all cancers. One out of four patients with breast cancer may develop cutaneous metastases. Breast carcinoma is responsible for two thirds of cutaneous metastasis in women. In men, cutaneous metastases of breast carcinoma are extremely rare. Different mechanisms underlie the appearance of skin metastases in breast carcinoma: direct extension, vascular or lymphatic spread, and iatrogenic implantation of malignant cells following a surgical procedure (mastectomy or reconstruction).

Clinical Features

Cutaneous breast metastases usually appear on the chest wall (at the site of mastectomy) (Fig. 71.1), axilla, abdomen, and scalp. They are less common on the back, upper arms, and lower abdomen. Rarely, they can also be seen on the buttocks, perianal region, lower extremities, and eyelids. The most common presentation is solitary or multiple papules and/or nodules (Fig. 71.2). Much rarer, they can present as telangiectatic carcinoma, erysipeloid carcinoma, carcinoma en cuirasse, alopecia neoplastica (Fig. 71.3), acute paronychia, pyogenic granuloma, vasculitis, and zosteriform lesions. Telangiectatic carcinoma appears as nodules, papules, or purpuric plaques with prominent telangiectasias or lymphangioma circumscriptum-like pseudovesicular lesions on the chest wall in the proximity of the surgical scar. Erysipeloid or inflammatory carcinoma presents as warm and tender, sharply demarcated erythematous plaques and patches that simulate erysipelas. Carcinoma en cuirasse or scirrhous carcinoma presents as indurated erythematous plaques that infiltrate the chest wall mimicking morphea or localized scleroderma. Zosteriform or herpetiform metastasis is a very rare form of presentation with papules, vesicles, nodules, or blisters that affect individual dermatomes, mimicking herpes zoster. Alopecia neoplastica may present as one or more bluish or violaceous, indurated alopecic plaques.

Pathology

In general, the histological features of the metastases are similar to those of the primary tumor, although metastases may exhibit less differentiation. Histological variants include a glandular pattern, an Indian file pattern of malignant cells in between collagen fibers

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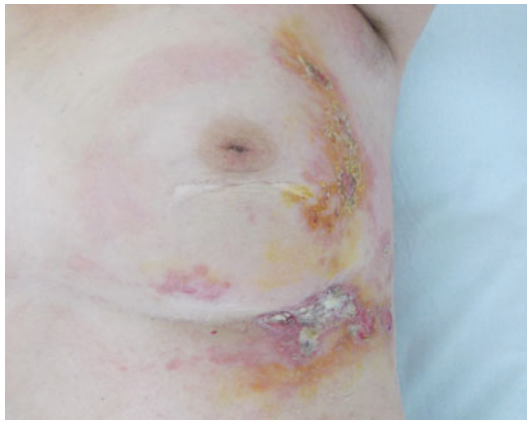

Fig. 71.1 Cutaneous metastases of breast carcinoma. Warm, erythematous patches and plaques surrounding the sectorectomy scar for breast carcinoma

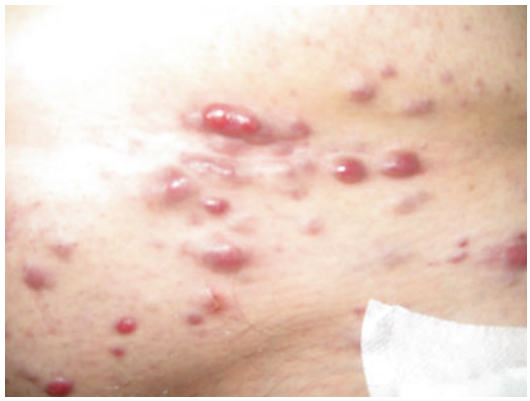

Fig. 71.2 Cutaneous metastases of breast carcinoma. Multiple tumors with a vascular appearance disseminated on chest and abdomen in a patient with breast cancer

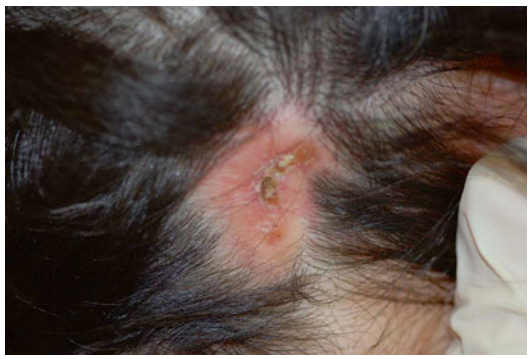

Fig. 71.3 Cutaneous metastases of breast carcinoma-alopecia neoplastica. Erythematous indurated alopecic plaque on the scalp of a patient with breast carcinoma

(Fig. 71.4a, b), lymphatic embolization by malignant cells, a fibrotic pattern, and an epidermotropic pattern (Fig. 71.5a, b). Inflammatory metastatic carcinoma shows deposition of malignant cells in superficial and/or deep lymphatics accompanied by a slight inflammatory infiltrate. Telangiectatic carcinoma displays aggregations of malignant cells in both lymphatics and blood vessels and many dilated blood vessels in the papillary dermis. Sclerodermoid metastatic lesions present with tumoral deposits accompanied by a fibrotic stroma. Carcinoma en cuirasse shows prominent fibrosis within which the few tumor cells usually encountered can be easily overlooked. Nodular metastases of breast carcinoma tend to display masses of tumor cells (Figs. 71.6 and 71.7), although some may also show a linear distribution of tumor cells in between collagen bundles. In alopecia neoplastica, the pilosebaceous units are destroyed by either neoplastic cells or fibroplasia.

The following basic antibody panel should be used whenever confronted with a suspicion of cutaneous metastatic breast carcinoma: ER, PR, mammaglobin, GCDFP-15, and Her-2/neu. Most cutaneous metastatic breast cancers exhibit positivity for CK7, GCDFP-15, mammaglobin, CAM5.2, CEA, ER, and BerEP4 and negativity for CK20. Occasionally, there is loss of CK7 and/or gain of CK 20. In triple negative cases, staining for at least one of the three markers—mammaglobin, GCDFP-15, and androgen receptor—is supportive of a breast primary.

Differential Diagnosis

Currently, there is no single marker with high enough sensitivity and specificity to make a clear distinction between a cutaneous metastasis of breast carcinoma and a primary cutaneous adnexal tumor. This differentiation is still based on clinical grounds. Unlike primary cutaneous adnexal tumors, cutaneous metastases usually develop rapidly, over a course of weeks to months, and often there are multiple lesions. Development of a panel of immunostains to aid in this distinction

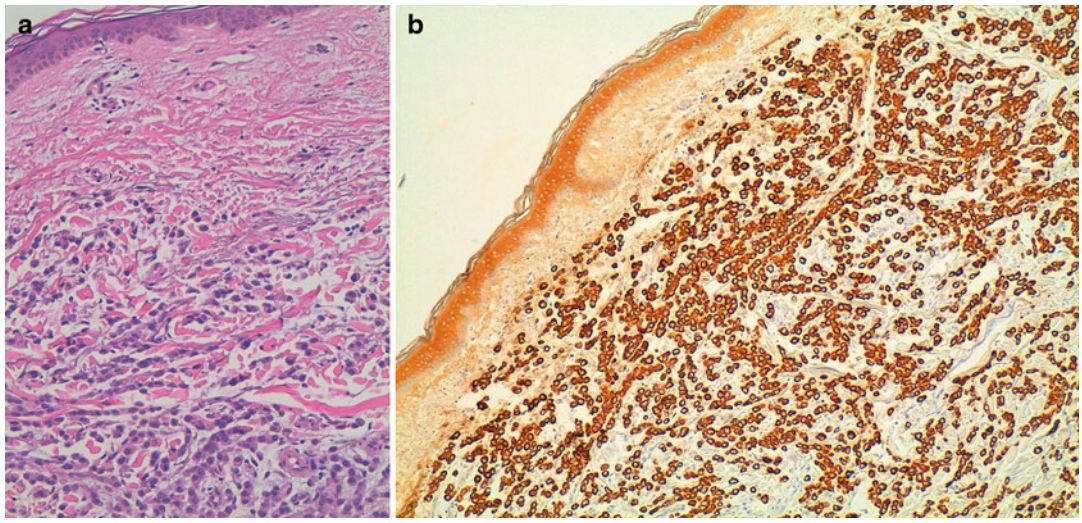

Fig. 71.4 Cutaneous metastases of breast carcinoma. (**a**) Indian file pattern. (**b**) Positivity of tumor **cells** for **cytokeratin AE1/AE3**

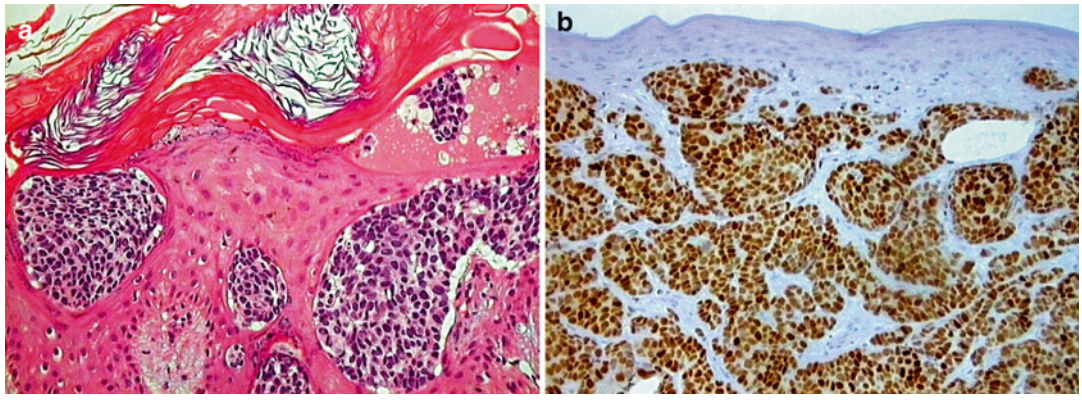

Fig. 71.5 Cutaneous metastases of breast carcinoma. (**a**) Epidermotropic metastasis. (**b**) Tumor **cells** are **estrogen receptor positive**

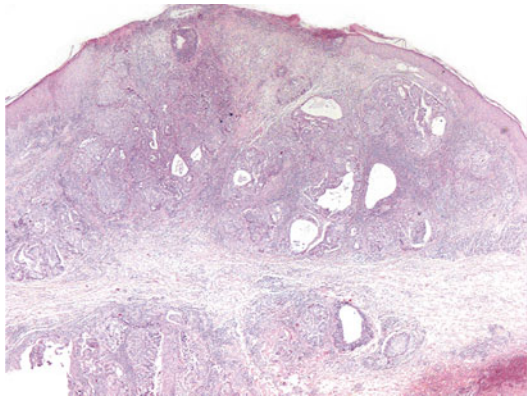

Fig. 71.6 Cutaneous metastases of breast carcinoma. Both nodular and glandular pattern are seen

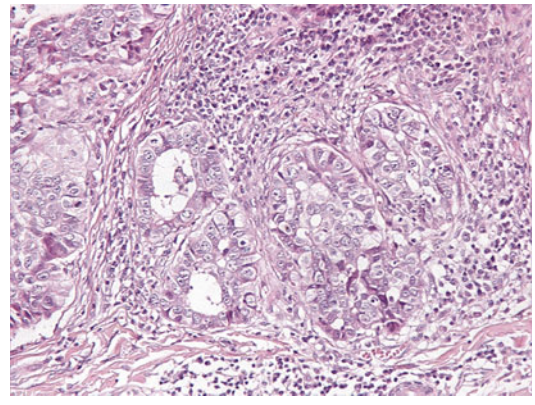

Fig. 71.7 Cutaneous metastases of breast carcinoma. Masses of poorly differentiated cells are admixed with aggregates of more differentiated cells

has been an area of extensive research. So far, the following markers have been used in different studies with some success: mammaglobin, p63, CK5/6, CK5, CK14, CK 15, CK17, D2-40, and calretinin. Positivity for mammaglobin and negativity for p63, CK15, and D2-40 are in favor for a metastatic breast carcinoma.

Metastatic histiocytoid breast carcinoma shows aggregations of relatively bland, uniform, histiocytic-like adenocarcinoma cells that may mimic a xanthoma, xanthelasma, or a histiocytoma. However, careful scrutiny usually shows more typical tumor cells exhibiting a characteristic "Indian file" pattern. Metastatic adenocarcinoma of the breast may also present with signet-ring cells, albeit rarely, and thus may initially suggest stomach or intestinal origin. As some metastatic tumors from the breast may show pronounced epidermotropism, they can be misinterpreted as melanoma. Cutaneous metastases from breast cancer may also display an adenoid cystic pattern which may be very difficult to differentiate from the primary cutaneous adenoid cystic carcinoma. Cutaneous metastases of metaplastic breast cancer may mimic a primary malignant cutaneous mixed tumor.

Prognosis

The prognosis of patients with cutaneous metastasis depends upon the type and biological behavior of the underlying primary tumor. As a rule, the appearance of cutaneous metastases implies a poor prognosis. However, they do not always portend a fulminant course.

Treatment

Surgical excision may be considered for solitary lesions. In general, inflammatory carcinoma and carcinoma en cuirasse are resistant to local therapy. Hormone receptor (ER, PR)-positive breast cancer patients may benefit from hormonal therapy. Chemotherapy with anthracycline-containing regimens, methotrexate/5-fluorouracil, methotrexate/5-fluorouracil/cyclophosphamide, taxanes, and gemcitabine may be used in cases with rapidly progressive cutaneous metastases or concurrent visceral determination. Trastuzumab, a monoclonal antibody, may be of benefit for tumors that overexpress the Her2-*neu* protein. The following investigational agents are currently used in clinical trials: photodynamic therapy, miltefosine, and antiangiogenesis agents.

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Cutaneous Metastases of the Gastrointestinal Tract

72

Irina Margaritescu

Introduction

Cutaneous secondaries from colorectal cancers are infrequent, occurring in less than 4 % of patients, with the more common sites of disseminated disease being the liver, lung, bone, and brain. However, being such common cancers, colorectal cancers are still common causes of cutaneous metastases. Thus, in both men and women, colorectal carcinoma is the second most common source of cutaneous metastases. In men, the most common source of gastrointestinal (GI) tract cutaneous metastases is the large intestine cancer (19 %), followed by squamous cell carcinoma of the oral cavity (12 %), stomach cancer (6 %), and esophageal cancer (3 %). Gastric adenocarcinomas (ADC) account for the vast majority (95 %) of gastric tumors and are more prevalent in men. Gastric ADC usually metastasizes to the liver, peritoneal cavity (Blumer's shelf), intra-abdominal lymph nodes, ovary (Krukenberg's tumor), and supraclavicular lymph nodes. By contrast, cutaneous metastases are very rare.

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Clinical Features

The most common site of cutaneous spread from colorectal primaries is the abdominal wall, specifically the area of previous surgical incisions. Usually, the cutaneous metastases appear after the primary tumor has been recognized. Direct extension via surgical tracts or dissemination via lymphatics accounts for this type of metastases. Remote lesions involving the upper and lower extremities, the head and neck regions (including face and tongue), and the scrotum have also been documented. Most of these occur in the presence of widely metastatic disease and are likely due to hematogenous spread. Very rarely, remote cutaneous metastases are the initial presentation of metastatic disease. Typically, the lesions present as solitary or multiple, firm, non-ulcerating nodules. They can be sessile, pedunculated, or grouped, with a vascular or cystic appearance. Varying morphological patterns have been reported, albeit rarely: inflammatory carcinoma, zosteriform metastases, cicatricial metastases, alopecia neoplastica, and inflammatory nodules, abscesses, ulcers, and draining sinuses in the perianal area mimicking hidradenitis suppurativa.

Cutaneous metastases from gastric adenocarcinoma usually follow the diagnosis of gastric carcinoma by several months or years. Very uncommonly they may be the presenting sign of the internal cancer. As with colorectal carcinoma, gastric adenocarcinoma metastazing to the skin usually involves the abdominal region on the area of previous

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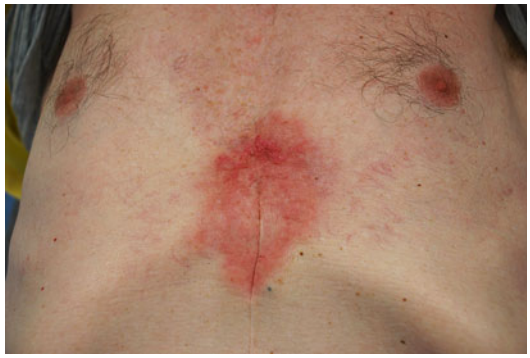

Fig. 72.1 Cutaneous metastases from gastric carcinoma. An erythematous plaque around a scar from excision of a primary neoplasm

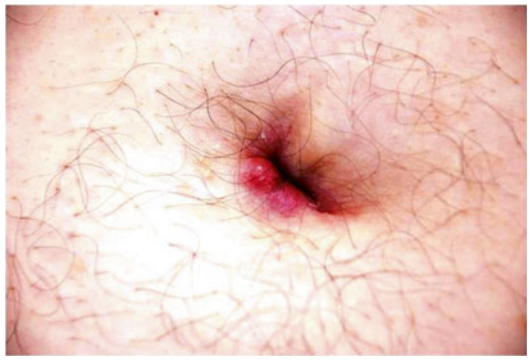

Fig. 72.2 Cutaneous metastases from colon adenocarcinoma. Sister Mary Joseph's periumbilical nodules

surgery (Fig. 72.1), including the umbilicus (Sister Mary Joseph's nodule) (Fig. 72.2). Less common sites include the breast, eyelids, eyebrow, back, face, scalp, neck, upper extremities, chest, axilla, shoulders/arms, and perianal region. Cutaneous lesions have a wide variety of clinical appearances. However, the most typical presentation is with multiple asymptomatic, firm, well-delineated red, plum-colored or hyperpigmented nodules, several centimeters in size. Uncommonly, metastases adopt a zosteriform distribution or an erysipelas-like pattern and can produce scaring alopecia. The lesions may be misdiagnosed as epidermal cysts, pyogenic granulomas, hemangiomas, neurofibromas, or condylomata.

Classically, gastric cancers have been associated with umbilical nodules (so-called Sister Joseph nodules). These are named after the surgical assistant of St. Mary's Hospital at the Mayo Clinic, Sister Mary Joseph, who first noticed the development of an indurated umbilical nodule in the setting of gastric cancer. However, these umbilical metastases may come from tumors other than the stomach, like ovary, colon, rectum, or pancreas. The primary site remains unknown in almost 30 % of cases. The mechanisms of metastasis include contiguous infiltration and spread via the blood or lymphatic vessels.

Skin metastases from oral cavity cancers are almost always squamous cell carcinomas. They usually occur in men and arise at the site of surgery for the primary tumor. Apart from the head and neck region, they may appear at remote sites like back or elbow. They usually present as multiple nodules, but they can also appear as ulcers. As they usually appear on the head and neck region, differentiation from primary cutaneous squamous cell carcinoma can be very difficult.

Cutaneous metastases from esophageal cancer are extremely rare. Most reported esophageal cancers were squamous cell carcinoma, but there were some case reports of skin metastases from esophageal adenocarcinoma. As with other internal cancers, cutaneous metastases from esophageal cancer may present as solitary or widespread nodules. Reported sites of involvement include scalp, finger, and axilla.

Pathology

Histologically, skin metastases from colorectal carcinoma tend to present with well-differentiated, often mucin-secreting, glandular structures (Figs. 72.3 and 72.4). Sometimes, due to abundant mucin secretion, a mucinous carcinoma-like pattern may be encountered. Other histological variants include: papillary, signet-ring cell, adenoid cystic, and anaplastic variants. Carcinoids may show different histological patterns depending on the original site of the tumor: trabecular pattern is usually associated with stomach carcinoids, nodular pattern is associated with carcinoids originating in the small intestine, and proximal colon and mixed pattern with the distal colon and rectum carcinoids. Some metastases may display a pronounced epidermotropism.

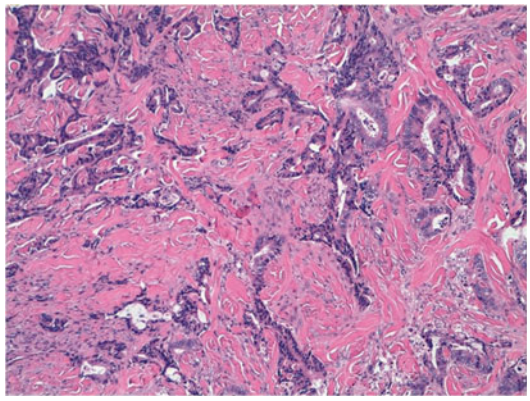

Fig. 72.3 Cutaneous metastases from colon adenocarcinoma (Sister Mary Joseph's nodule). Infiltrating atypical glandular structures

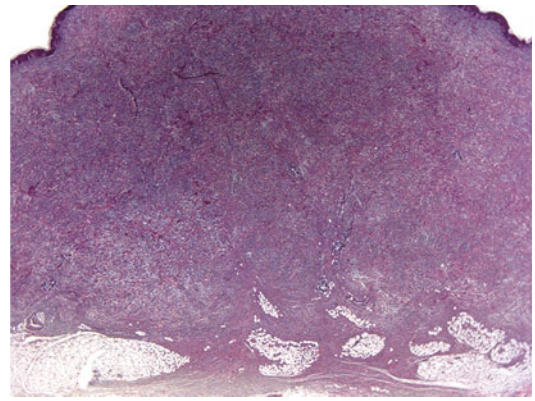

Fig. 72.5 Cutaneous metastases from gastric carcinoma. Diffuse masses of neoplastic cells occupying the whole dermis and extending into the subcutaneous fat

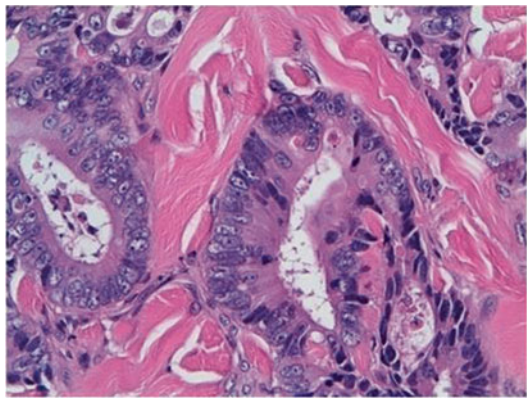

Fig. 72.4 Cutaneous metastases from adenocarcinoma of colon. Atypical glandular structures with mitotic figures

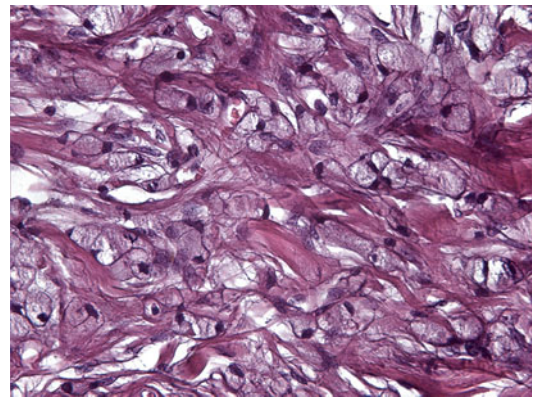

Fig. 72.6 Cutaneous metastases from gastric carcinoma. Signet-ring appearance of the cells suggests gastric origin

The great majority of gastric tumors are gastric adenocarcinomas classified as papillary, tubular, mucinous, and signet-ring cell carcinomas. Skin metastases display varying degrees of histological differentiation. The tumors may show signet-ring cells dispersed individually or in small groups at the level of the dermis and hypodermis (Fig. 72.5). Signet-ring appearance of the cells may serve as a clue for a gastric or intestinal origin of the tumor (Fig. 72.6). However, they may also be present in metastases from carcinoma of the lung or breast. Likewise, a mucinous carcinoma-like pattern is suggestive of gastrointestinal origin. Nevertheless, a same pattern may be encountered in primary mucinous carcinoma of the skin or in mucinous skin metastases arising from other internal cancers, like the lung, salivary gland, lacrimal gland, esophagus, or breast cancers.

Cutaneous metastases from oral cavity and esophagus cancers are usually squamous cell carcinomas.

Immunohistochemistry: Cutaneous metastases from colorectal adenocarcinomas express the following immunoprofile: CK20+, CAM5.2+, CK19+, CEA+, Cdx2+, CA19.9+, BerEP4+, and CK7 (occasionally rare positive cells). Cutaneous metastases from gastric adenocarcinomas display the following immunoprofile: CK7+ (Fig. 72.7), CK20+, CAM5.2+, CK19+, Cdx2+ (Fig. 72.8), CA19.9+, BerEP+, and MUC-5AC+.

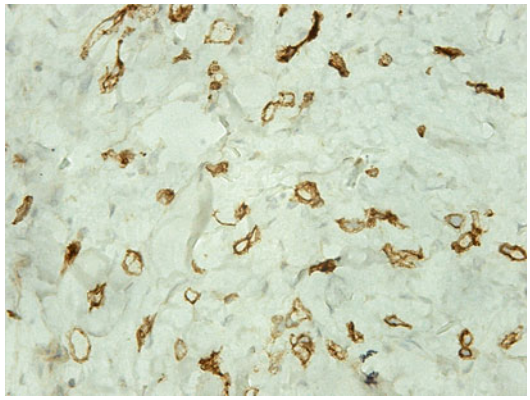

Fig. 72.7 Cutaneous metastases from gastric carcinoma. The neoplastic cells are positive for CK7

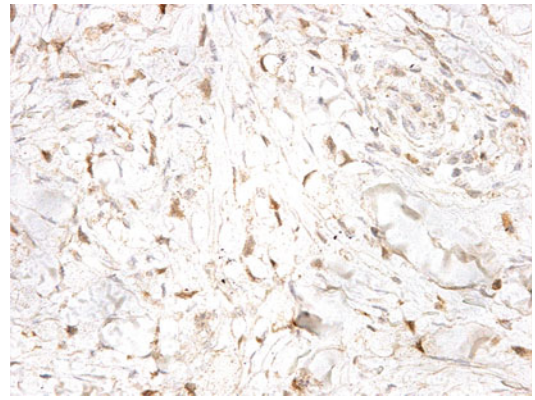

Fig. 72.8 Cutaneous metastases from gastric carcinoma. The neoplastic cells display week and diffuse positivity for Cdx2

Differential diagnosis: Given the completely different prognosis and management, cutaneous metastases from GI tract cancers should be differentiated from primary cutaneous sweat gland carcinomas and primary cutaneous squamous cell carcinomas. This can be achieved through very close clinicopathologic correlation coupled with imaging studies. The same protocol should be used to exclude cutaneous metastases from other internal organs. An adequate immunohistochemical panel can point to the site of the primary tumor.

Prognosis

In general, cutaneous metastases from GI tract are associated with a poor prognosis and mortality. The prognosis is dependent on the primary cancer type and different treatments used. In colorectal cancer with cutaneous metastases, the average survival is 18 months. The survival time is no longer than few months in cases of cutaneous metastases from esophageal cancer.

Treatment

Solitary lesions can be treated by surgical excision. In widespread disease, chemotherapy and radiotherapy can be used but only as a palliative measure.

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Cutaneous Metastases of Lung Cancer

73

Irina Margaritescu

Introduction

Lung cancer is the most common tumor that metastasizes to the skin in men. In women, it represents the third cause of cutaneous metastases. The most common involved sites are the anterior trunk and the head and neck regions, followed by the abdomen, the back, the lower limb, and the upper limb. The development of cutaneous metastases usually follows the diagnosis of lung cancer. Rarely, they may be the presenting sign.

Clinical Features

The most common form of presentation is isolated or multiple nodules (Fig. 73.1). Other morphological presentations include: inflammatory carcinoma (Figs. 73.2, 73.3 and 73.4), alopecia neoplastica, "clown nose," subungual metastases mimicking paronychia or glomus tumor, zosteriform metastases, carcinoma en cuirasse, and telangiectatic cutaneous metastasis.

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Pathology

Histologically, undifferentiated lung cancer (Fig. 73.3) is the type that most frequently metastasizes to the skin (50 %), followed by adenocarcinoma and squamous cell carcinoma (30 % each). The following histological patterns of pulmonary cutaneous metastases are usually seen: undifferentiated, adenocarcinoma, and squamous cell carcinoma. Much less commonly, bronchiolar carcinoma, mucoepidermoid carcinoma, carcinoid, pulmonary sarcoma, small cell carcinoma, or the rare intravascular bronchioalveolar tumor may be seen. Cutaneous metastases may also display signet-ring cells and an adenoid cystic carcinoma-like pattern.

Immunohistochemistry: Metastases from lung adenocarcinoma display the following immunoprofile: CK7+, CK20 usually negative, CAM5.2+, CEA+, TTF1+, and BerEP4+. Metastatic cutaneous squamous cell carcinoma of the lung is positive for CK5/6, CK 19, and CEA and negative for CK7, CK20, CAM5.2, TTF1, and BerEP4. Metastatic small cell carcinoma of the lung stains with low-molecular-weight cytokeratin in a diffuse perinuclear pattern and variably with antibodies against neurofilament.

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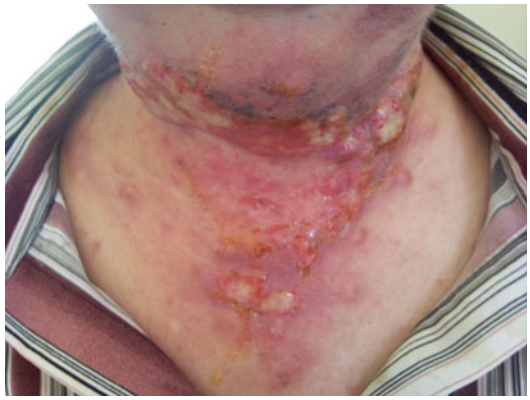

Fig. 73.1 Multiple isolated nodules over the neck and chest area from a lady with known lung carcinoma

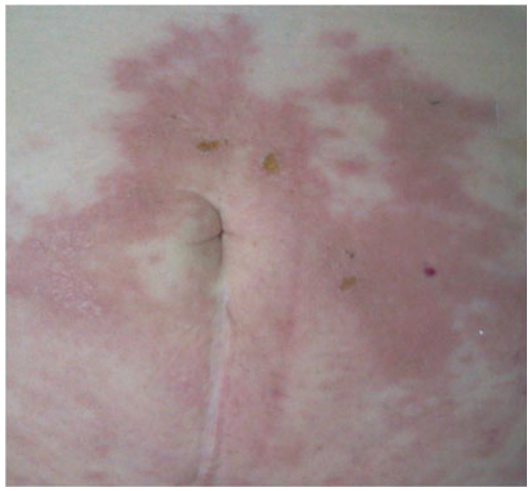

Fig. 73.2 Cutaneous metastases of lung carcinoma. Skin metastases can rarely present as inflammatory carcinoma

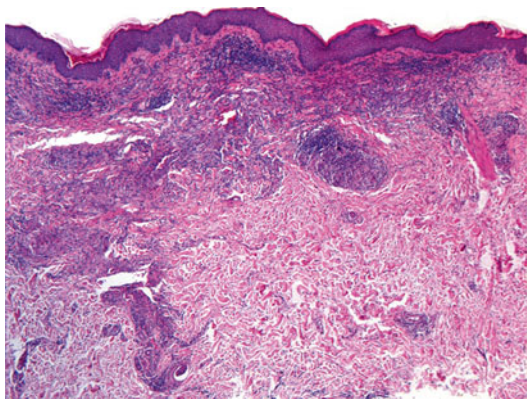

Fig. 73.3 Cutaneous metastases of lung carcinoma. Tumoral deposits of lung adenocarcinoma in the dermis accompanied by an abundant inflammatory infiltrate

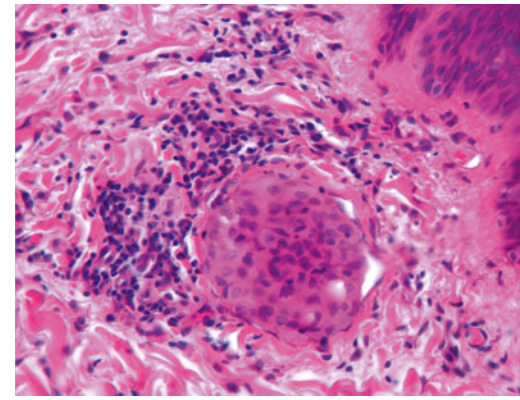

Fig. 73.4 Cutaneous metastases of lung carcinoma. Typical inflammatory carcinoma with tumoral deposits in dilated lymphatics

Differential Diagnosis

Cutaneous metastases from an adenocarcinoma of the lung should be differentiated from basal cell carcinoma, porocarcinoma, eccrine spiradenoma, hidradenoma, and cutaneous endometriosis. Metastases of a squamous cell lung carcinoma of the lung should be differentiated from a primary cutaneous squamous cell carcinoma. Cutaneous metastasis of neuroendocrine small cell carcinoma may mimic the small cell subtype of cutaneous neuroendocrine carcinoma (Merkel cell carcinoma). Merkel cell carcinoma usually expresses CK20 in a dot-like nuclear pattern and is negative for TTF1, whereas bronchial neuroendocrine carcinoma is negative for CK20 and stains positive for TTF1. However, there are exceptions to the rule. Immunohistochemical and ultrastructural studies are necessary to distinguish metastatic small cell carcinoma of the lung from lymphoma cutis, melanoma, neuroblastoma, primitive neuroectodermal tumor, rhabdomyosarcoma, and metastatic Ewing's sarcoma.

Prognosis

The appearance of cutaneous metastases in patients with lung cancer usually signifies a poor prognosis, with an average survival up to 6 months.

Treatment

Patients with cutaneous metastasis of lung cancer have an extremely poor prognosis, despite aggressive combinations of chemotherapy and radiation therapy. In general, only palliative chemotherapy (combinations of cisplatin and etoposide or cyclophosphamide, adriamycin, and vincristine) with or without radiotherapy is indicated for these patients. Some patients will receive only supportive palliative therapy.

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Cutaneous Metastases of the Kidney and Urogenital System

74

Franco Rongioletti

Cutaneous Metastases of the Kidney

Introduction

Renal cell carcinoma is the third most common neoplasm of the genitourinary tract, being clear cell carcinoma the most common type (60 % of the cases with an incidence peak between 50 and 70 years). The incidence of cutaneous metastases from the kidney varies from 3 % to 6 %. Cutaneous metastases occur late, and a mean lapse of 63 months from the diagnosis of renal cell carcinoma may occur. The main cutaneous sites are the head and scalp followed by the chest and the abdomen.

After the kidney, the most common sites of cutaneous metastases from genitourinary tract malignancies include the bladder and the prostate with an overall incidence of about 3 %. Skin metastases from genitourinary tract malignancies tend to involve the abdominal region as preferential site.

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Clinical Features

The most common clinical presentation is characterized by asymptomatic, pink to red to purplish, angiomatous subcutaneous nodules mimicking vascular lesions (Figs. 74.1 and 74.2). Flesh-colored to brown nodules and plaques, acral or subungual metastases, involvement of operative scars from previous nephrectomy or of the site of puncture of needle biopsy, pulsatile mass, cutaneous horn, or diffuse nodular involvement covering 20 % of body surface have also been described.

Pathology

Almost all cases are of clear cell histological type with tumor cells containing abundant glycogen and some lipids. There is often a grenz zone with uniform polyhedral, atypical clear cells arranged in compact, trabecular, tubulocystic, alveolar, or papillary configurations (Figs. 74.3 and 74.4). Prominent vessels and red blood cell extravasations with hemosiderin deposits in the stroma are common features. Neoplastic cells are positive for vimentin, cytokeratins AE1/AE3 (Fig. 74.5a), and MNF116. CD10, the common acute lymphoblastic leukemia antigen, is expressed in 89–100 % of renal cell carcinoma (Fig. 74.5b) and is a useful marker to distinguish cutaneous metastatic renal cell carcinoma from primary cutaneous adnexal carcinomas with eccrine and

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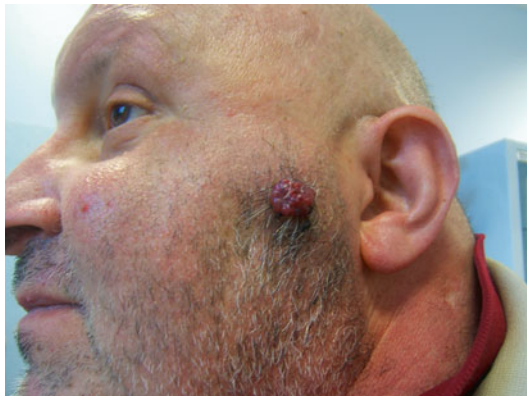

Fig. 74.1 Cutaneous metastases from clear cell carcinoma of the kidney. The most common clinical presentation is characterized by asymptomatic, *pink* to *red* to *purplish*, angiomatous subcutaneous nodules mimicking vascular lesions

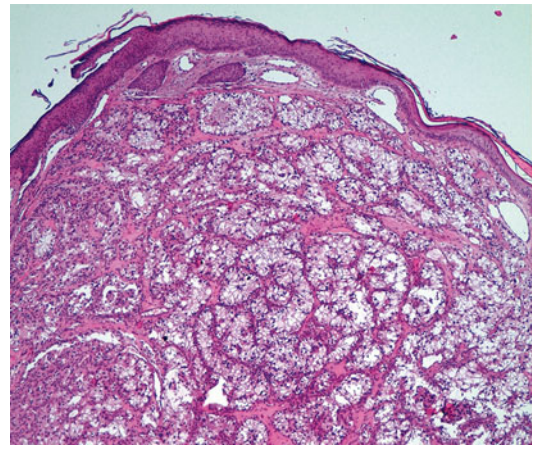

Fig. 74.3 Cutaneous metastases from clear cell carcinoma of the kidney. Under a grenz zone, there are uniform polyhedral, atypical clear cells arranged in trabecular and alveolar configurations

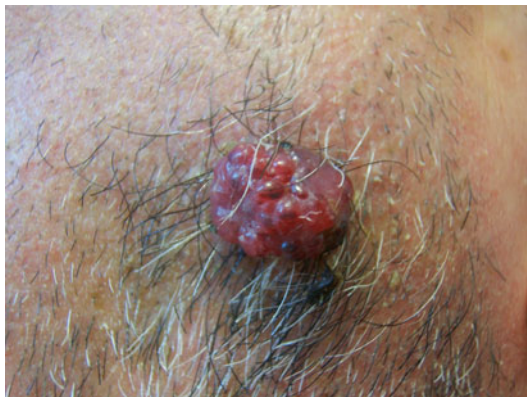

Fig. 74.2 Cutaneous metastases from clear cell carcinoma of the kidney. Close-up of angiomatoid skin metastasis

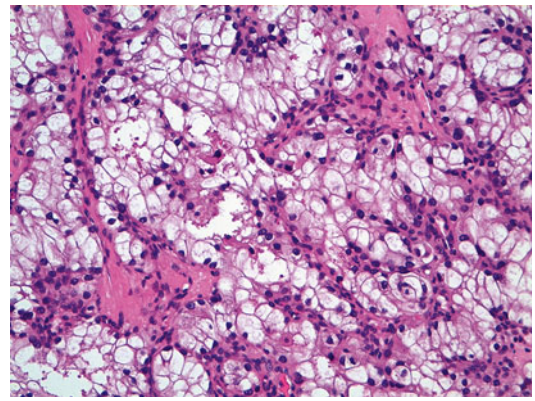

Fig. 74.4 Cutaneous metastases from clear cell carcinoma of the kidney. Clear cell histological type with tumor cells containing abundant glycogen

apocrine differentiation. Renal cell carcinoma marker (RCC-Ma) is another marker which is expressed in 79.7 % of primary renal cell carcinoma (96 % of papillary variants) and whose expression is highly specific (98 %) for metastatic renal cell carcinoma. PAX2 and especially PAX8 are diagnostically useful markers for both primary and metastatic renal neoplasms of different histological types.

Differential Diagnosis

Because of the prominent vascular supply of renal cell carcinoma, cutaneous metastases are known to have an angiomatous appearance that mimics pyogenic granuloma, hemangioma, Kaposi sarcoma, and Kaposi sarcoma. It is important to consider skin metastasis in case of new onset tumors with a vascular appearance in

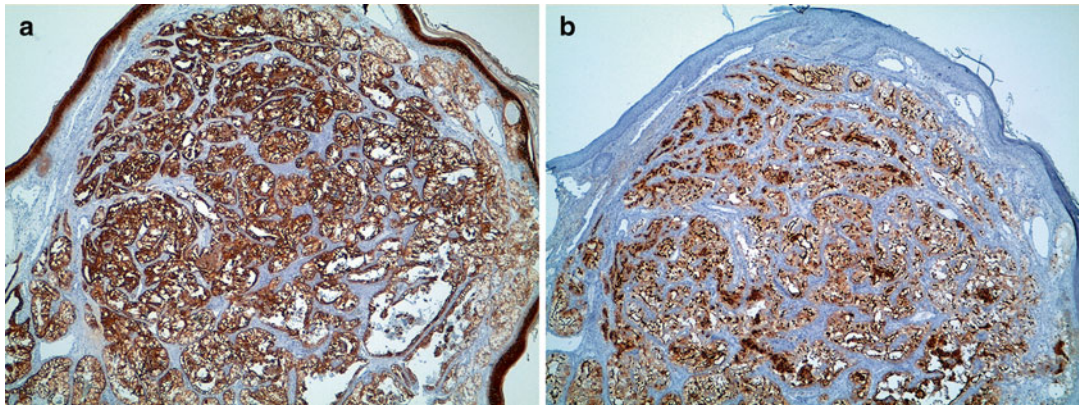

Fig. 74.5 Cutaneous metastases from clear cell carcinoma of the kidney. (**a**) Neoplastic cells are positive for cytokeratins AE1/AE3 (**b**) and CD10

the head and neck region of patients with associated renal malignancy. Histologically, all clear cell tumors of the skin enter the differential diagnosis. RCC-Ma is an immunohistochemical marker that is mostly expressed by renal cell carcinoma and is negative in other clear cell tumors of the skin. Adipophilin, a marker expressed in neoplasm with sebaceous differentiation, is also positive in cutaneous metastases from renal cell cancer.

Prognosis

Metastatic cutaneous renal cell carcinoma is generally regarded as a late manifestation of the disease leading to a poor prognosis with a median overall survival rate of approximately 6–9 months. Clinicopathologic parameters of the primary renal cell carcinoma that are associated with a better prognosis include size less than 5 cm in diameter; lack of diffusion to the collecting system, perirenal fat, or regional lymph nodes; and a predominance of clear cells.

Treatment

Chemotherapeutic treatments are unsatisfactory, with maximal partial response rates of 5–20 % reported. The use of new therapeutic agents directed towards aberrant molecular pathways such as tyrosine kinase inhibitors (sorafenib, sunitinib) or antiangiogenic substances, such as VEGF receptor antagonists, has shown antitumor activity and clinical benefit. For palliative treatment of skin metastases, surgical excision of solitary skin lesions, radiotherapy alone or combined with surgery, or intralesional injection of therapeutic agents such as interferon has been used with variable results. Curiously, in the appropriate setting, surgical excision of isolated cutaneous metastases using Mohs surgery has been proposed.

Cutaneous Metastases of the Urogenital System

After the kidney, the most common sites of cutaneous metastases from genitourinary tract malignancies include the bladder and the prostate with an overall incidence of about 3 %. Skin metastases from genitourinary tract malignancies tend to involve the abdominal region as preferential site. Generally, the clinical presentations are characterized by noninflammatory or inflammatory nodular lesions, fibrotic/sclerodermoid lesions, and lobulated, ulcerated, and bleeding masses. Most of the bladder tumors metastasizing to the skin are urothelial carcinomas (transitional cell carcinomas). Neoplastic cells similar to transitional cells are usually seen arranged in solid cords and nests or grouped within dilated dermal

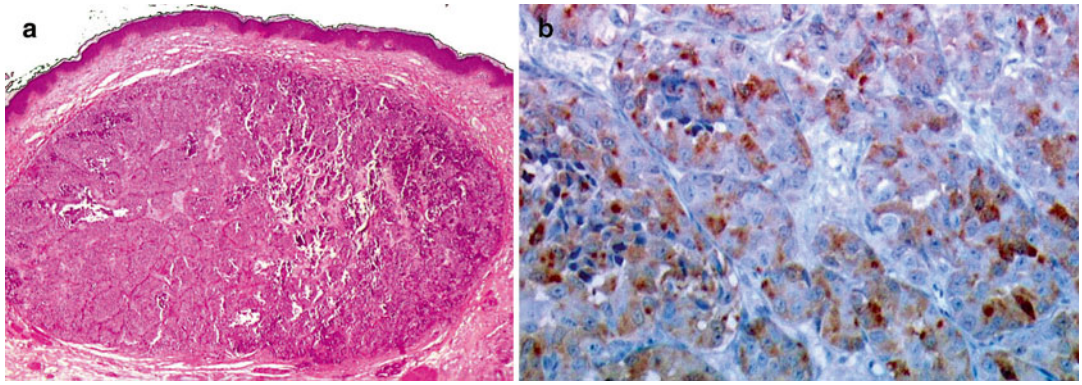

Fig. 74.6 Cutaneous metastases from prostate. (a) Dermal nodular metastasis consisting of undifferentiated cells partially arranged in glandular structures and solid cords. (b) The metastasis is positive for prostate-specific antigen (Courtesy of Jean Kanitakis, Lyon, France)

lymphatic vessels. The CK20+/CK7+/CA125+ immunophenotype is highly characteristic of transitional cell carcinoma of the urinary bladder. Prostate cancer is the leading cause of death from malignancy in men over 75 years of age. Forty percent of patients with primary prostate cancer have metastases at the time of diagnosis, and the bone is the most frequently involved site. However, prostate cancer metastatic to the skin is rare and represents 1 % of all cutaneous metastases in men. It is usually an adenocarcinoma with high affinity to the suprapubic region that seems to have a better prognosis than that of metastases from kidney or bladder cancer. Histopathologically, dermal metastases consist of undifferentiated cells partially arranged in glandular structures and solid cords with diffuse stromal infiltration of single cells and necrosis (Fig. 74.6a). The metastases are positive for prostate-specific antigen (Fig. 74.6b), prostate acid phosphatase, CK903/34 beta E12/high-molecular-weight cytokeratin, and ERG transcription factor (in 50 % of cells). The median time of survival is less than 6 months from the appearance of the cutaneous metastases.

Skin metastases are uncommon in gynecologic cancers. Cutaneous metastases develop in 3.5–4 % of patients with ovarian cancer and are associated with poor prognosis with a mean survival of 4 months. Histologically, islands of well-differentiated adenocarcinoma or serous papillary cystoadenocarcinoma of the ovary are seen in the dermis. The cells are usually CK7+/CA125+/CK20-. Cervical carcinoma is still one of the most common malignancies in women, and its incidence of skin metastases seems to be higher in cervical adenocarcinoma and undifferentiated carcinoma than in squamous cell carcinoma. Immunohistochemically, adenocarcinoma of endocervix is usually positive for CK7 and negative for CK20. Additional rare cutaneous metastases originate from uterine leiomyosarcoma, endometrial or papillary serous cancer, and squamous cell carcinoma of the uterus.

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Miscellanea of Cutaneous Metastases

75

Franco Rongioletti

Cutaneous metastases of thyroid gland

Clinical Features

The occurrence of skin metastases from thyroid gland tumors is a rare event, although thyroid carcinoma is the most common endocrine malignancy. Papillary and follicular carcinomas are the most common type of tumors metastasizing to the skin; less frequently, anaplastic and medullary carcinomas are the culprit. Skin metastases arise with equal frequency in both sexes with a mean age of 65 years. Metastases present with single or multiple flesh-colored to reddish or violaceous papules and nodules that may ulcerate. The head, neck, and scalp are the most common sites of involvement. Other sites include post-thyroidectomy scar and sacral skin.

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Pathology

Skin metastases recapitulate the primary tumors. Papillary carcinomas consist of complex, branching papillary structures with fibrovascular cores and psammoma bodies. The tumor shows tubules lining colloid-like material which is positive with PAS stain (Figs. 75.1–75.3). Crowded, cuboidal cells with large, oval pale nuclei with a grooved irregular contour and containing eosinophilic inclusions line the papillae. A strong association of BRAF mutation with lymph node metastasis, extrathyroidal extension, and disease recurrence has been confirmed in papillary thyroid cancer. Follicular carcinoma is characterized by multiple solid islands of epithelial cells arranged in follicles and containing colloid. A follicular-related variant called insular carcinoma presents with solid cords and nests made by small, round, and regular cells with occasional microfollicles and is associated with a more aggressive course (Fig. 75.4). Immunostaining usually reveals reactivity to thyroid transcription factor and thyroglobulins (Fig. 75.5). Differently from papillary and follicular carcinomas, thyroglobulin is usually negative in the anaplastic variant, but PAX8 is usually positive. The last histopathologic type in frequency is metastatic medullary thyroid carcinoma that arises from C cells of the thyroid and often appears in the setting of multiple endocrine neoplasia syndrome. Neoplastic cells are positive for calcitonin.

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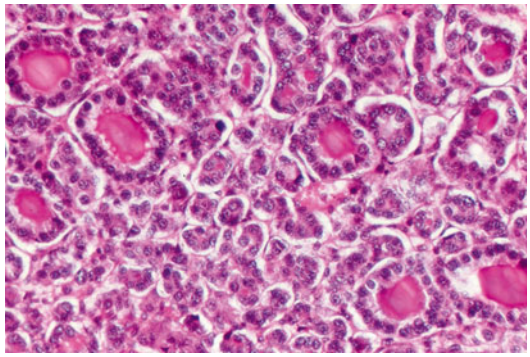

Fig. 75.1 Skin metatstasis from a primary papillary thyroid carcinoma (courtesy of B.Cribier, Strasbourg, France)

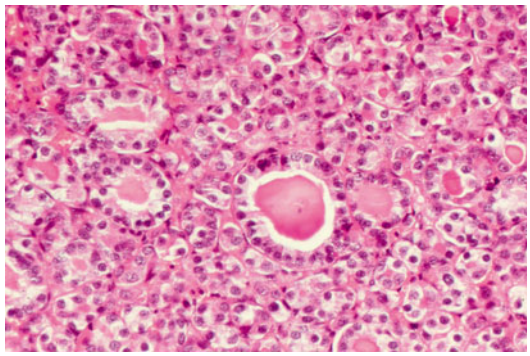

Fig. 75.2 The skin tumor is composed of tubules containing colloid-like material and lined by cells with nuclear grooves. (courtesy of B.Cribier, Strasbourg, France)

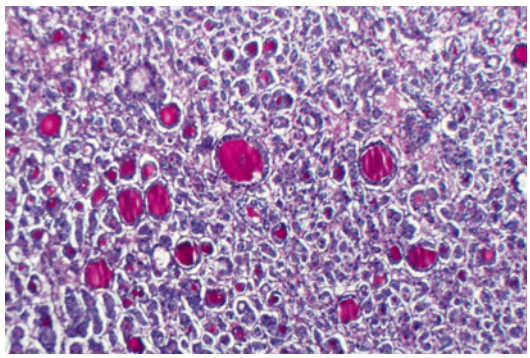

Fig. 75.3 The tumor is positive with PAS stain(courtesy of B.Cribier, Strasbourg, France)

Differential Diagnosis

Twenty-nine to 45 % of skin lesions are not suspected of being metastases due to an unusual clinical presentation. Common clinical diagnoses which are weighed are nonmelanoma skin cancer, cutaneous lymphoma, and cutaneous sarcomas.

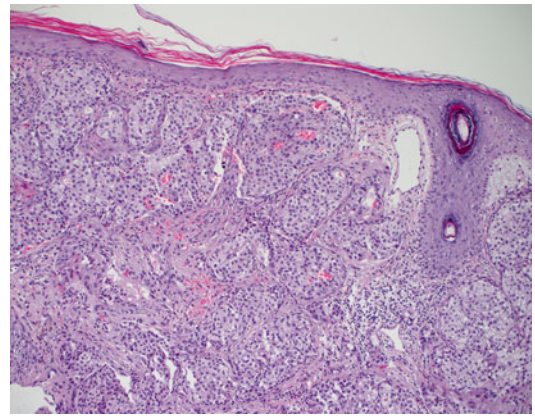

Fig. 75.4 Skin metastasis from a primary insular carcinoma, a follicular-related variant of thyroid carcinoma. Note solid cords of round or oval monotonous cells surrounded by fibrovascular septa (courtesy of W.Kempf, Zurich, Switzerland)

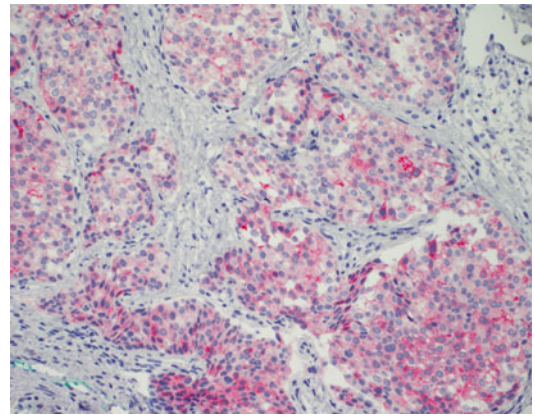

Fig. 75.5 Immunostaining reveals reactivity to thyroglobulins

Prognosis

Skin metastases from thyroid malignancies are manifestations of advanced disease, independently from the histological types. Age over 45 years and follicular pathology were significant predictors of a poorest outcome. In the setting of follicular carcinoma, patients with extracutane-

ous involvement at the time of cutaneous metastasis may have a worse prognosis than those with isolated cutaneous metastases. The average length of survival after cutaneous metastasis is 19 months.

Treatment

Surgical approaches are generally the most effective as a palliative measure for single cutaneous metastasis. However, excision of select metastases does little to increase survival. Targeted therapy such as with sorafenib has shown promise in the treatment of patients with advanced or metastatic thyroid carcinoma when external beam radiation and radioiodine (131I) therapy are not suitable or give poor outcomes.

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Additional Tumors and Patterns of Cutaneous Metastases

Laryngeal carcinoma is common in males (96 % of cases) around the age of 40 years. Skin metastases appear as solitary or multiple nodules on the head and neck region or occasionally as erythematous infiltrating plaques on the supraclavicular and infraclavicular regions. The tumor is made of malignant squamous cells arranged in solid/nesting patterns and is reactive for cytokeratins (AE1/AE3) and p53.

Sarcoma metastases to the skin are relatively rare, because most involve the deep organs such as the lung, liver, or deep soft tissues. Leiomyosarcoma is the most common source, and the scalp is the most frequent site. The skin is the initial site of metastasis in only 1–3 %, while the majority of patient with skin metastases from sarcomas harbor metastases elsewhere.

Cancer of unknown primary site (synonym: occult primary malignancy) is defined as the presence of a skin metastasis when a primary site or tissue of origin has not been possible to identify despite an intensive diagnostic approach. Its incidence is between 2 % and 6 %, and men are more often diagnosed. Only 10–20 % can primarily be discovered while 50–75 % are found only by autopsy. In 15–25 %, the primary site remains unknown even on postmortem examination. The primary sites in order of frequency include: the lung (5–35 %), pancreas (15–20 %), liver and biliary tract (10–15 %), colon (3–8 %), and kidney (3–5 %).

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Angiosarcomas

Elisa Cinotti, Franco Rongioletti

Cutaneous angiosarcoma is a rare, aggressive vascular sarcoma that occurs in three main different clinical settings: classic cutaneous angiosarcoma arising in sun-damaged skin of elderly patients, cutaneous angiosarcoma associated with chronic lymphedema, and post radiation angiosarcoma. Recent studies have shown that high-level amplification of *MYC* oncogene seems to be specific for radiation and lymphedema-associated angiosarcoma. A new histological variant has been named pseudolymphomatous cutaneous angiosarcoma. In general, cutaneous angiosarcoma carries a poor prognosis, associated with 5-year overall survival rates between 10 and 30 %.

Pseudolymphomatous angiosarcomas

Synonyms: Angiosarcoma with prominent lymphocytic infiltrate.

Introduction: Pseudolymphomatous cutaneous angiosarcoma, described by Requena *et al*. in 2007, is characterized by a prominent inflammatory lymphoid infiltrate that can mask the underlying vascular malignant proliferation and mimic a lymphomatous process.

Clinical features: It presents with the same clinical features as the classical angiosarcoma, as a bruise-like areas or erythematous-violaceous nodule or plaque of the scalp, face and breast (Fig. 1). Three cases resembled facial rosacea, one case developed seven years after breast radiotherapy. Rongioletti *el al*. described a collision tumor with a basal cell carcinoma, and a transformation of an histologically-classical cutaneous angiosarcoma in a pseudolymphomatous type in a recurrence after surgical excision and radiotherapy. In one case, the accompanying dense inflammatory infiltrate was attributable to a superimposed infection by *Pseudomonas aeruginosa*.

Pathology: It is characterized by the same atypical vessels of the classical angiosarcoma, with the addition of a prominent inflammatory lymphoid infiltrate between the vessels, obliterating some or most of the channels (Fig. 2). The infiltrate can be diffuse or can be organized in lymphoid follicles with germinal centers scattered within the diffuse lymphoid infiltrate. Vessels are poorly circumscribed, irregularly dilated, and anastomosing, lined by prominent, atypical endothelial cells (Fig. 3, 4) that usually express CD31 (Fig. 5), CD34, and D2-40. Most of the cells of the lymphoid infiltrate express strong immunoreactivity for CD3, CD4, CD5, and CD45 markers, whereas only scattered cells express CD8. Most of the lymphocytes of the germinal centers are positive for CD20, CD21, CD79a, and Bcl-6 whereas Bcl-2 can be detected in the cells of the mantle zone.

Differential diagnosis: The main histological differential diagnoses are: (1) cutaneous B-cell follicle center lymphoma, (2) pseudolymphoma, (3) Kimura's disease/angiolymphoid hyperplasia with eosinophilia (ALHE), and (4) Kaposi sarcoma.

Pseudolymphomatous angiosarcoma can mimic both cutaneous lymphoma and pseudolymphoma, and the recognition of irregular anastomosing vascular spaces lined by prominent endothelial cells among the lymphocytic infiltrate allows the correct diagnosis. In particular, among lymphomas the differential diagnosis is mainly with cutaneous follicle center B-cell

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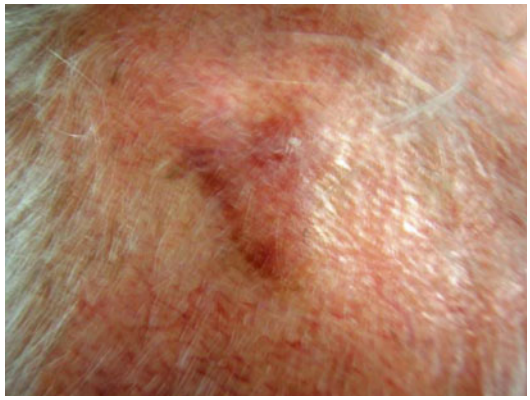

Fig. 1 Pseudolymphomatous cutaneous angiosarcoma. An erythematous-violaceous plaque with bruise-like features on the forehead

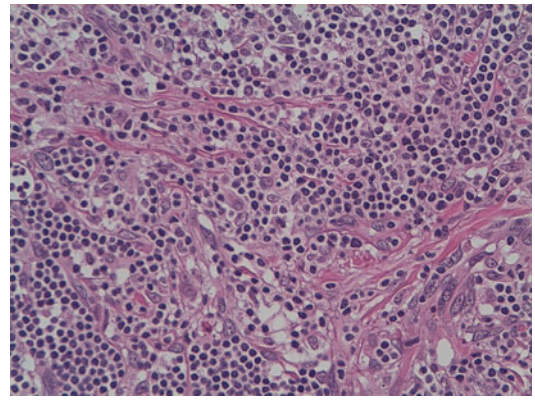

Fig. 4 Pseudolymphomatous cutaneous angiosarcoma The atypical cells are obscured by the dense lymphoid infiltrate

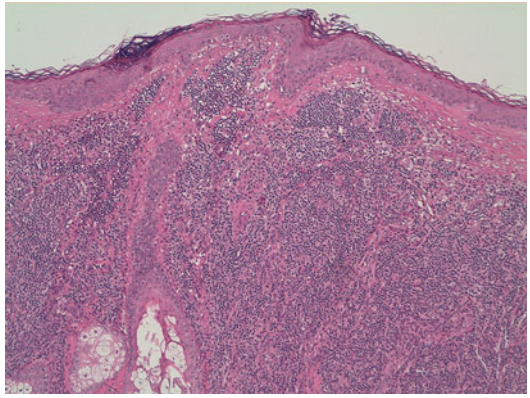

Fig. 2 Pseudolymphomatous cutaneous angiosarcoma. A prominent inflammatory lymphoid infiltrate between the vessels, obliterating some or most of the channels

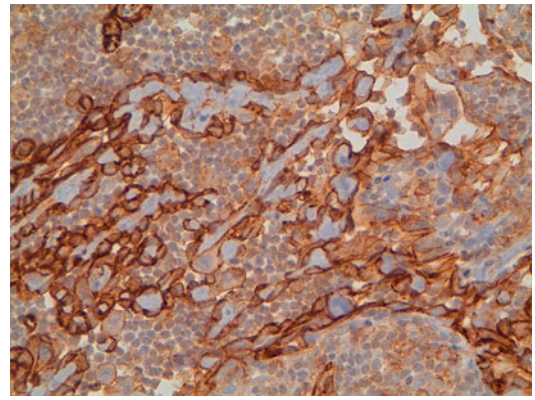

Fig. 5 Pseudolymphomatous cutaneous angiosarcoma The atypical endothelial cells are outlined by CD31 expression

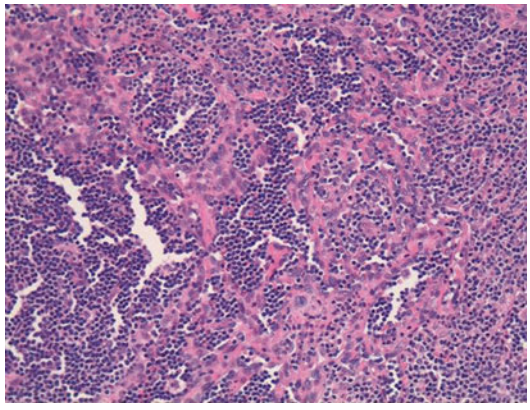

Fig. 3 Pseudolymphomatous cutaneous angiosarcoma At higher magnification, vessels are poorly circumscribed, irregularly dilated, and anastomosing

lymphoma where the infiltrate can be diffuse and/or organized in follicles. The demonstration of a clonal rearrangement of heavy-chain immunoglobulin can help the diagnosis. Kimura's disease/ALHE shows a more or less diffuse lymphoid infiltration with lymphoid follicles and germinal centers in the presence of thick-walled blood vessels lined with “epithelioid” or “histiocytoid” endothelial cells protruding into the lumen. The presence of eosinophils and the absence of atypical cytologic features of the endothelial cells are clues for Kimura's disease/ALHE. A spindle-cell component and clusters of eosinophilic hyaline globules may help to distinguish Kaposi sarcoma.

Prognosis: Cutaneous angiosarcoma is believed to have the worst prognosis *quoad vitam* among malignant skin tumors, with an overall 5-year survival rate ranging from 12% to 20% (median survival 18–28 months). Two cases series have showed a better prognosis of the pseudolymphomatous variant with either longer survival or increased disease-free intervals, and less frequently metastases. However, further studies are necessary to confirm the relatively better prognosis of pseudolymphomatous variant of cutaneous angiosarcoma.

Treatment: Early wide surgical excision of the tumour is the treatment of choice. The efficiency of adjuvant radiotherapy has not been established.

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