Primary Cutaneous Lymphomas

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Key Points

- The diagnosis of a PCL consists of a synoptic integration of clinical and biological data and must rely upon a comprehensive clinico-pathological correlation as a pivotal element in the diagnostic approach.
- Immunohistochemistry represents a highly valuable tool in order to determine the neoplastic nature of a cutaneous lymphoid infiltrate and to distinguish different lymphoma histotypes.
- The finding of B- or T-cell clonality, yet in the absence of morphological and immunohistochemical clues indicative of malignancy, should always be carefully considered and makes follow-up of the patient more intensive.
- Thanks to the joint effort of expert representatives of the EORTC cutaneous lymphoma study group and the WHO classification, a new classification WHO/EORTC was developed in 2005.
- Mycosis fungoides and primary cutaneous CD30-positive lymphoproliferative disorders represent the most common type of cutaneous T-cell lymphomas.
- Cutaneous B-cell lymphomas (CBCL) account for approximately 20–25 % of all primary cutaneous lymphomas. The most common histotypes is represented by cutaneous marginal zone B-cell lymphoma and cutaneous follicle centre lymphoma.

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Main Problems in Evaluating Lymphoid Infiltrates of the Skin

The majority of lymphocytic infiltrates in the skin have noticeable common characteristics. Most infiltrates are of T-cell origin, represent reactive conditions and are not characterised by either significant cytologic or pattern atypia.

These infiltrates are immunologically driven and are the result of cytotoxic mechanisms or delayed-type hypersensitivity and antibody-related cellular immunity. Indeed, they appear more frequently in patients with underlying iatrogenic and/or endogenous immune dysregulation.

Examples of such benign conditions are comprised under the chapters of *spongiotic and*

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exematous dermatitis (allergic contact dermatitis and photoallergic reactions), *interface dermatitis* (erythema multiforme, acute graft vs. host disease, lichenoid dermatitis, with special regard to lichenoid drug eruptions and subacute cutaneous lupus erythematosus) or *diffuse and nodular lymphocytic* d*ermal infiltrates* (polymorphous light eruption, non-scarring discoid/tumid lupus erythematosus, morphea, Jessner lymphocytic infiltrate of the skin).

Indeed, conditions of persistent lymphoid reactions may be characterised by either cytological atypia, thus mimicking lymphoma and potentially becoming biologically unstable, or by exhibiting clonal restriction and phenotypic aberrancy and therefore acquiring a limited tendency toward progression to overt lymphoma. Among these conditions are lymphoid reactions, which may resemble lymphoma. In reality, they are expressions of exuberant responses to immune dysregulation, both B- and T-lymphocyte proliferations, namely, the so-called lymphocytoma cutis, lymphomatoid drug eruptions, lymphomatoid lesions in collagen vascular diseases, primary cutaneous plasmocytosis and viral-associated lymphomatoid dermatitis.

Increased risk of malignant transformation in lymphoid proliferations following sustained activation of the immune system is strictly related to genetic instability of lymphocytes. Chronic infections, immunodeficiency status and autoimmune disorders favour mechanisms of clonal selection of transformed lymphocytes. The persistence of the trigger acts through different pathogenetic mechanisms, thus increasing proliferation and decreasing apoptosis. Selective advantages given to lymphoid clones may gain independence from antigen stimulation.

A model of infection-driven B-cell lymphoproliferation in the skin is represented by the activation of marginal zone lymphocytes by *Borrelia burgdorferi*, consequently giving rise to borrelial lymphocytoma and possibly to marginal zone lymphoma of the skin with pathogenetic mechanisms analogous to those described by other extranodal lymphomas, i.e. gastric MALT lymphoma associated to *Helicobacter pylori*, splenic marginal zone lymphoma associated with HCV infection and ocular adnexal MALT lymphoma associated with *Chlamydia psittaci infection*.

In regard to T-cell proliferations, an example of atypical lymphoid growth is displayed by lymphomatoid drug eruptions.

The molecular demonstration of clonality and of aberrant immunoprofile is not unusual in such conditions, and this data must be carefully taken into consideration when performing final diagnosis.

Recognition of antigen-mediated lymphoid proliferation is of the utmost importance to avoid the misdiagnosis of overt lymphoma and overtreatment. This is because withdrawal of the antigens responsible for the immune reaction and/or treatment of the immune dysregulation may lead to regression of the disease.

On the other hand, detection of oligoclonality or monoclonality, with or without loss of T antigen in the setting of morphological atypia, although not mandatorily leading to a diagnosis of malignancy, still represents an alarming condition. Such lesions should be identified as cutaneous lymphoid T-cell dyscrasia and in a small percentage of cases can progress to cutaneous T-cell lymphomas. This group of disorders encompasses a constellation of distinct entities (pityriasis lichenoides, pigmented purpuric dermatosis, syringolymphoid hyperplasia with alopecia, alopecia mucinosa, large plaque parapsoriasis and idiopathic erythroderma) and some inflammatory conditions which can present phenotypic abnormalities, mainly loss of CD7 and CD62L expression, most often observed in overt T-cell lymphomas.

On these basis, it is easy to understand that the differential diagnosis of a dense cutaneous lymphoid infiltrate characterised by morphological atypia, possibly accompanied by aberrant phenotype and clonal expansion or restriction, may still represent one of the most challenging problems in dermatopathology, despite advances in molecular pathology and immunohistochemistry. A final diagnosis consists of a synoptic integration of clinical and biological data and must rely upon a comprehensive clinicopathological correlation as a pivotal element in the diagnostic approach.

The main issues when facing a cutaneous lymphoid infiltrate are the following:

- To discriminate between reactive and neoplastic proliferation, with special regard to early neoplastic conditions.
- To identify reactive lesions more prone to developing malignancy.
- To identify the histotype of the neoplastic growth, which may be strictly correlated to specific clinical outcome.
- To distinguish primary diseases from concurrent and secondary skin involvement. In fact, the former have a favourable clinical behaviour and do not require aggressive treatment. Concurrent cutaneous B-cell lymphomas, involving other lymphoid and/or extranodal sites, present clinico-pathological and prognostic features much closer to primary ones.
- To discriminate between the different histological patterns of lymphomas linked to the age of the lesions and of the disorder itself (mycosis fungoides, for example, may show extremely heterogeneous clinical presentation and long history of smouldering lesions before there are overt manifestations of the disease).

Concerning the differential diagnosis between reactive and neoplastic lesions, the main cause of misinterpretation, making exclusion of malignant lymphoma possible to render only on morphological basis, encompasses the following items:

- Skin is by itself a natural homing for T-lymphocytes and exocytosis/epidermotropism of lymphocytes is a common finding.
- Morphological findings, especially in inflammatory disease, depend on the age of the lesion biopsied.
- Cytological atypia is not a hallmark of malignancy in skin lymphoid disorders. Presence of lymphocytes with "blastic" size and alarming nuclear features is a frequent finding in reactive disorders as well. These cells often express CD30 molecule as an activation marker without diagnostic implications.
- Cellular monomorphism, which is of paramount help in nodal lymphomas, is useless in the skin, where most of all indolent B-cell lymphomas display marked cellular pleomorphism.
- Predominance of a reactive population overwhelming the neoplastic growth is frequent in indolent B-cell lymphomas.
- In contrast to the nodal counterpart, the architectural pattern of growth can be of little help in both reactive and neoplastic entities.
- Immunomarkers like CD10 and BCL2 are very useful in the differential diagnosis between reactive germinal centres and follicular lymphomas in the lymph node, but results most often negative in the cutaneous counterpart, especially in early lesions.

Most Frequent Diagnostic Challenges in Everyday Practice

Benign Lymphoid Hyperplasia of the Skin and Cutaneous B-Cell Lymphoma

Cutaneous lymphoproliferative infiltrates with follicular growth pattern may be follicular lymphomas, marginal zone lymphomas or lymphoid hyperplasia of the skin (B-cell pseudolymphomas).

Besides clinical differences among these entities, there are morphological clues, together with immunophenotypical and molecular features, which can denote the distinctions.

According to Leinweber et al. [1], the main criteria suggestive of follicle centre lymphoma are:

- Absence of tingible body macrophages within follicles
- Reduced proliferation rate detected by immunohistochemistry
- Absence of the polarisation of the follicles evaluated with the aid of MIB-1
- Presence of small clusters of CD10- and/or Bcl6-positive cells outside the follicles
- Positivity for Bcl2 within follicular cells
- Monoclonality for JH chain of immunoglobulin, investigated by PCR

Cases presenting at least four of the mentioned criteria are considered to be malignant.

Additional features pointing to malignancy suggested by other authors [2] are as follows:

- Extensive expression of CD20 by cells showing loss of CD79a expression
- Equal kappa and light chain-restricted populations, potentially indicating an emerging lambda light chain-restricted population
- Absence of T-cell receptor-β (TCR-β) gene rearrangement due to the fact that T-cell clonality is not uncommonly detected in reactive disorders

The differential diagnosis is more difficult when dealing with cutaneous lymphoid hyperplasia and marginal zone lymphoma [3, 4] since these two disorders share similar clinical findings. Indeed, they both affect women more than men and present single or multiple slowly developing nodules involving the face, back and upper extremities. Morphologically, both entities may present reactive follicles; variable pattern of infiltration (diffuse, nodular, lichenoid and perivascular in different pattern combinations), either a bottom-heavy or top-heavy infiltrate; and the presence of a "grenz" zone.

More distinctive features for marginal zone lymphoma are:

- Aggregates or sheets of marginal zone cells
- Sheets or zones of plasma cells
- Lymphoepithelial lesions in the sweat and sebaceous glands
- Monotypic plasma cells
- Lysis or disintegration of CD23 or CD21 network of follicular dendritic cells
- B-cell/T-cell ratio ≥3:1
- Presence of IgH gene rearrangement

More distinctive features of cutaneous lymphoid hyperplasia are:

- Epidermal changes (focal spongiosis, with parakeratosis and exocytosis)
- Polytypic plasma cells with kappa/lambda <4/1
- Absence of IgH gene rearrangement

Primary Follicle Centre Lymphoma and Primary Marginal Zone Lymphoma of the Skin

The immunophenotypical profile is most important in differentiating these two entities. The typical differential features are the following:

- In primary follicle centre lymphoma the neoplastic cells are Bcl2−, Bcl6−, CD10+/− and CD23+/−
- Monotypic plasma cells are mostly located at the periphery of the infiltrate and are a major diagnostic criterion for marginal zone lymphoma [5]
- In marginal zone lymphoma the neoplastic cells are Bcl2+, BCL6−, CD10− and CD23−

Moreover clusters of CD123+ plasmocytoid dendritic cells are constantly observed in marginal zone lymphoma and not in other primary cutaneous lymphomas [6].

Marginal Zone Lymphomas with Marked Plasmacytic Differentiation and T-Cell-Rich Background Versus Peripheral T-Cell Lymphoma Versus Primary Cutaneous Plasmocytosis Versus Cutaneous Involvement by Castleman's Disease

More recently some authors have drawn attention to a variant of marginal zone lymphoma with marked plasmacytic differentiation and T-cell-rich background which had already been described by Magro et al. [7] and had been historically diagnosed as primary cutaneous immunocytoma or primary cutaneous plasmacytoma.

In the absence of a history of plasma cell myeloma, the diagnosis of cutaneous plasmacytoma should be made with great caution, and the presence of any lymphoid follicles, B cells or follicular dendritic cells in the infiltrate will lead to the exclusion of it.

Notwithstanding the notion that a T-cell component represents a phenomenon frequently reported in different primary cutaneous lymphoma, the occurrence in this variant of a marginal zone lymphoma of atypical-looking T-lymphoid cells that are small to medium in size, which may obscure the neoplastic B-cell proliferation, may lead to misdiagnosing peripheral T-cell lymphoma or mycosis fungoides.

Molecular study of IgH and TCR gamma gene rearrangement may be warranted to confirm the results.

Clinico-pathological studies have demonstrated that the T-cell-rich variants of marginal zone lymphoma have no prognostic implications.

Primary cutaneous plasmocytosis is a rare entity, sometimes occurring in concomitance with endocrinopathies and frequently accompanied by polyclonal hypergammaglobulinemia, which represents an analogy to mucosal-based plasmocytosis like Zoon's balanitis and plasma cell orofacialis. Polyclonality of plasma cells is mandatory for diagnosis.

Skin lesions associated with Castleman's disease are mainly in the context of POEMS syndrome. The histopathological findings consist of atrophic germinal centres with prominent hyalinised vessels associated with sheet-like proliferation of plasma cells, which may or may not show evidence of light chain restriction. Typically, the infiltrate is deeply located in the dermis possibly extending to subcutaneous tissue.

Early Lesions of Primary Cutaneous Follicle Centre Lymphoma Diffuse Type Versus Diffuse Large B-Cell Lymphoma

Primary cutaneous follicle centre lymphoma is usually described as a diffuse proliferation of large B predominantly cleaved lymphocytes, admixed with centroblasts, infiltrating the dermis and possibly the subcutis.

In the lymph node, a diffuse pattern of growth in the context of a follicle centre lymphoma is considered a marker of progression of the disease and connected to a diagnosis of diffuse large B-cell lymphoma with implications in treatment and prognosis.

On the other hand, in the skin, the biological and clinical behaviour of a primary follicle centre lymphoma is not affected by the pattern of growth.

Some authors [8, 9] have described the clinico-pathological features of early lesions of primary cutaneous follicle centre lymphoma diffuse type featured by patchy and diffuse lymphoid proliferation with a tendency to collect in perivascular and/or periadnexal districts thus mimicking reactive infiltrates. Giulia et al. [9] describe for the first time in detail the clinico-pathological features of the early lesions of PCFCL diffuse variant, which actually represent the early manifestation of the so-called Crosti lymphoma of the back. They report a series of 24 patients with lesions located on back and shoulder (20 cases), arm (2 cases) and scalp (1 case). In most cases, the patients typically showed a larger infiltrated central lesion, surrounded by smaller papules or nodules sometimes far from the main affected area. All of them showed favourable outcome with radiotherapy following to surgical excision. Only one patient received chemotherapy. In three cases, the peripheral lesions underwent spontaneous regression, while in other cases recurrences happened. Biopsy specimens showed periadnexal and perivascular aggregates of small lymphocytes admixed with predominantly medium- to large-sized centrocytes and a minority of centroblasts. A follicular arrangement was never observed and CD21-positive dendritic reticular cells were fewer, and never clustered is commonly detectable in the follicular variant of this lymphoma. The authors suggest a different pathogenesis for this histotype and do not consider the diffuse variant as a progression of the follicular variant. Moreover, they stress the importance to distinguish it from diffuse large B-cell lymphoma leg type.

Diffuse Large B-Cell Lymphoma Versus Non-lymphoid Malignancies

Problems can arise in this differential diagnosis, in particular when appropriate tissue sampling is not provided or when the biopsy displays diffuse areas of necrosis or sclerotic band of collagen. Indeed, this group of disorders, including the leg type and the other types of NOS of diffuse large B-cell lymphomas, can be confused, at morphologic evaluation, with both T- and NK-cell lymphomas and with non-haematologic neoplasms. Merkel cell carcinoma and cutaneous metastatic carcinoma must be considered at times. The spindle cell variant of cutaneous diffuse large B-cell lymphomas (DLBCL) can be misinterpreted for spindle cell melanoma, spindle squamous cell carcinoma or spindle cell sarcomas. An extensive immunophenotyping of the neoplastic population

helps to avoid misdiagnosis because expression of lymphoid markers has never been described in non-lymphoid tumours.

Other challenging situations can be observed in cases in which the neoplastic large B cells are few and sparse, but it is important to be aware that their presence does not by itself point to malignant lymphomas. Expression by these cells of BCL6 and CD10 is a helpful hint to malignancy.

Early Mycosis Fungoides Versus Inflammatory Lichenoid Reactions/T-Cell Dyscrasias

The histopathological diagnosis of early lesions of mycosis fungoides may be impossible in some cases since morphological features are similar to those described in many inflammatory skin diseases involving the interface and the papillary dermis (psoriasis, chronic contact dermatitis, drug-induced lesions). Immunohistochemical studies are not distinctive.

The best suggestion remains to stem the diagnosis from the comprehensive integration of clinical, histopathologic, immunophenotypic and molecular data. Limited to histopathologic evaluation, the diagnosis of mycosis fungoides can be suggested only when applying strictly the morphologic criteria published by the EORTC cutaneous lymphoma study group [10]. In those cases in which histopathology results do not match with clinical diagnosis, the pathologist should not hesitate to ask for further biopsies.

Available Diagnostic Tools: Advantages and Pitfalls

Immunohistochemistry

Modern immunohistochemical techniques allow the study of the phenotypic signature of different lymphoproliferative entities on routinely fixed paraffin-embedded tissue sections. Immunohistochemistry thus represents a highly valuable tool in order to determine the neoplastic nature of an infiltrate and to distinguish different lymphoma histotypes.

CD20, CD79a and PAX5 are conclusive in recognising mature B-cell lineage, just as BCL6 and CD10 mark germinal centre derivation and cytoplasmic Ig reactions may display monotypic or polytypic Ig expressions.

The immunohistochemical profiles of the most common histotypes, which can be obtained using commercially available antibodies and which are reported in the WHO classification of primary cutaneous lymphomas, are illustrated in the following section.

Recently, a group of monoclonal antibodies on different primary B-cell lymphomas has been demonstrated to help in better defining specific antigenic profiles for research and possibly diagnostic purposes, since they are exclusively or preferentially expressed by specific histotypes, with regard to primary FCL and primary MZL. No specific set of monoclonal antibodies was found to label primary cutaneous DLBCL [11].

The expression of IgM, together with FOXP1 and BCL2, can be used as additional tool in the everyday practice for the differentiation between PCFCL and PCLDLB leg type, with this last entity constantly positive for all these three monoclonal antibodies [12].

The demonstration of antigen loss by using an extensive panel for T-cell lineage (CD2, CD3, CD4, CD5, CD7, CD8) can be of utmost aid in supporting the neoplastic nature of a lymphoid proliferation. In particular loss of CD2, CD3 and/or CD5 is more specific than loss of CD7, but still of low sensibility.

The evaluation of CD4/CD8 ratio is relevant for the differential diagnosis between early-stage mycosis fungoides and inflammatory disorders, together with CD1a immunolabeling. This latter marker can demonstrate tiny aggregates of Langerhans cells in the epidermis mimicking Pautrier abscesses and representing a usual finding in immunomediated reactive lesions.

It has to be remembered that special care has to be taken in the comprehension of CD4 expression by the investigated population, because CD4 is also a marker of histiocytes.

Granzyme B, perforin, CD56 and TIA-1 are good markers of cytotoxic activity and find a useful application in the signature of different conditions encompassed in the CD30 lymphoproliferative diseases spectrum, extranodal natural killer/T-cell lymphomas and subcutaneous panniculitis-like T-cell lymphomas.

It is important to keep in mind that aberrant expression of B-cell lineage marker can be observed in T-cell lymphomas, for example, MUM-1; the post-germinal centre activation marker is expressed by "activated large cells" in both lymphomatoid papulosis and anaplastic large-cell lymphomas [13].

In conclusion, one must keep in mind that immunohistochemical characterisation of lymphoproliferative skin disorders is of extreme relevance to complete and support the diagnosis but must be analysed in the context of the clinical and morphological setting.

Molecular Pathology

The most efficient molecular methods to analyse B-cell clonality of formalin-fixed, paraffin-embedded samples seem nowadays represented by BIOMED-2 PCR-based protocol [14] which allows to overcome the two main problems affecting sensitivity and specificity in this field of pathology [15].

Firstly, the common occurrence of somatic hypermutation in primer binding sites in primary cutaneous lymphomas often makes the binding of primers ineffective, and secondly, only small amount of neoplastic cells may be present in such cases of lymphomas.

BIOMED-2 PCR can theoretically detect 1–5 clonal lymphocytes in a population of 100 lymphocytes in which the remaining are benign. This implies a considerable risk of false-positive results in otherwise benign disorders (pseudomonoclonality and oligoclonality). Suggestions to improve efficacy and efficiency of molecular analysis are to confirm the results by duplicate or triplicate tests on the same sample and/or to perform laser microdissection of the hotspots.

On the contrary, false-negative or polyclonal results can occur more frequently in overt B-cell lymphomas and less in T-cell lymphomas.

Finally, it has to be remembered that dual lineage rearrangement is not a rare event in lymphoid infiltrates of the skin. Such lineal infidelity can affect both B- and T-cell lymphomas and leads to the conclusion that IgH and TCR gene analysis is not equivalent to B- or T-lineage assessment and has to be interpreted cautiously for diagnostic purposes.

The finding of T-cell clonality, yet in the absence of morphological and/or immunohistochemical clues indicative of malignancy, should always be carefully considered and makes follow-up of the patient more intensive.

Classification of Cutaneous Lymphomas

Early classification of lymphomas did not discriminate between nodal and extranodal forms of non-Hodgkin lymphomas and was mainly based on morphological and immunophenotypical features of the tumour cells. Most forms of cutaneous lymphomas were considered as skin involvement of systemic diseases and were treated according to this concept.

The EORTC classification published in 1997 represented the first consensus classification for primary cutaneous lymphomas [16]. It adopted biological concepts borrowed from the REAL classification, emphasising the importance of integrating clinical, histological, immunophenotypical and genetic findings in the diagnostic approach and definition of different nosological entities.

Based on the data collected from large cutaneous lymphoma registries such as the Lymphoma Registry in Graz and the Dutch Cutaneous Lymphoma Working Group, three main categories were identified by indolent, intermediate and aggressive clinical behaviour.

The REAL classification was updated by the WHO classification of lymphoid neoplasms published in 2001. This scheme includes most cutaneous T-cell lymphomas of the previous

Table 9.1 WHO/EORTC classification of cutaneous lymphomas

Mature T-cell and NK-cell neoplasms	Mature B-Cell neoplasms
Mycosis fungoides	Cutaneous marginal zone B-cell lymphoma (MALT type)
Pagetoid reticulosis (localised disease)	Cutaneous follicle centre lymphoma
Follicular, syringotropic, granulomatous variants	Cutaneous diffuse large B-cell lymphoma
Granulomatous slack skin	Intravascular large B-cell lymphoma
Sezary syndrome	Lymphomatoid granulomatosis
CD30+ T-cell lymphoproliferative disorders of the skin	Chronic lymphocytic leukaemia
Lymphomatoid papulosis	Mantle cell lymphoma
Primary cutaneous anaplastic large-cell lymphoma	Burkitt lymphoma
Subcutaneous panniculitis-like T-cell lymphoma	
Primary cutaneous peripheral T-cell lymphoma (PTL), unspecified	Immature haematopoietic malignancies
(Subtypes of PTL, provisional)	
Primary cutaneous aggressive epidermotropic	Blastic NK-cell lymphoma
CD8-positive cytotoxic T-cell lymphoma	CD4+/CD56+ haematodermic neoplasm
Cutaneous gamma-/delta-positive T-cell lymphoma	Precursor lymphoblastic leukaemia/lymphoma
Primary cutaneous small/medium CD4+ T-cell lymphoma	T-lymphoblastic leukaemia
Extranodal NK/T-cell lymphoma, nasal type	T-lymphoblastic lymphoma
Hydroa vacciniformia-like lymphoma (variant)	B-lymphoblastic leukaemia
Adult T-cell leukaemia/lymphoma	B-lymphoblastic lymphoma
Angioimmunoblastic T-cell lymphoma	Myeloid and monocytic leukaemias
	Hodgkin lymphoma

classification, while cutaneous B-cell lymphomas differ significantly from those identified by both the REAL and WHO classifications.

Indeed, notwithstanding the improvement given by the EORTC approach, this classification did not gain wide approval among pathologists and oncologists because it had led considerable confusion on the therapeutic approach.

Thanks to the joint effort of expert representatives of the EORTC cutaneous lymphoma study group and the WHO classification, a new classification (WHO/EORTC) was developed in 2005 [17]. This proposal was widely accepted by clinicians and pathologists and included in the currently adopted WHO classification published in 2008, which represents the nowadays general classification of nodal and extranodal lymphoid tumours worldwide adopted [18–20].

This review illustrates the salient features of the most common entities in the context of the recent WHO/EORTC classification of primary cutaneous lymphomas (Table 9.1).

Mature T-Cell and NK-Cell Neoplasms

Mycosis Fungoides and Subtypes

Clinical features: Mycosis fungoides (MF) represents the most common type of cutaneous T-cell lymphomas. It has been classified according to the type of skin lesions (patches, plaques and tumours), the presence or absence of large-cell transformation and/or extracutaneous involvement. It pursues an indolent clinical course with slow progression, and sometimes, subsequent biopsies are needed for a proper diagnosis, especially in the early manifestations of the disease. The male to female ratio is 2:1 with adults/elderly mostly affected. Skin lesions vary from large erythematous patches preferentially involving non-sun-exposed areas to reddish brown infiltrated plaques with wrinkled surface, to nodules solitary or generalised, sometimes ulcerated. A combination of patches, plaques and tumours is common in the well-developed

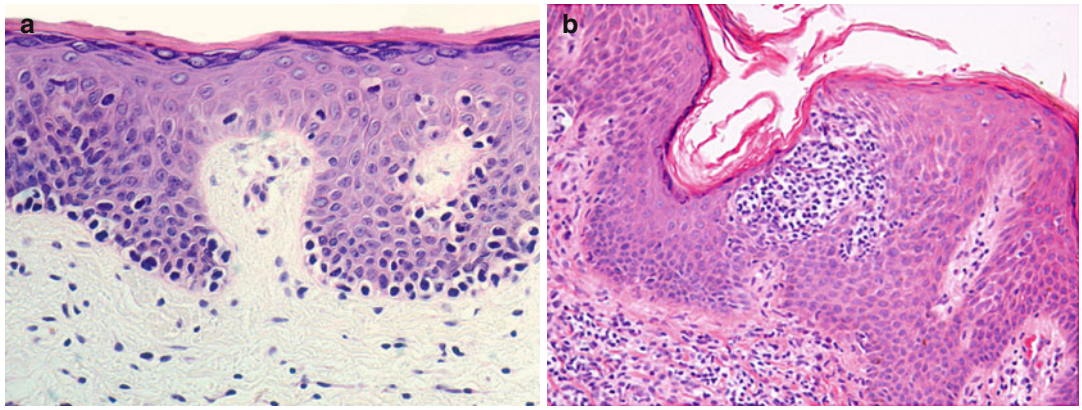

Fig. 9.1 Mycosis fungoides, patch stage. (**a**) Atypical lymphocytes arranged along the interface line. (**b**) Intraepidermal collection of atypical cells forming Pautrier microabscess

disease. Large-cell transformation occurs in more than 50 % of tumour stage MF. The most frequent sites of extracutaneous involvement in the later stages of the disease are lymph nodes, lung, spleen and liver. Several clinical variants of MF have been described. Some of them represent distinct clinico-pathological entities, while others are peculiar kind of skin involvement described by case reports. MF is rare in childhood (0.5–5 % of all cases) and presents mainly with early-stage lesions sometimes with concurrent or prior history of pityriasis lichenoides chronica. Sezary syndrome (SS) is actually considered an aggressive form of peripheral T-cell lymphoma involving elderly adults which may be or not preceded by idiopathic erythroderma and presents with generalised lymphadenopathy and pruritic erythroderma. The disorder is characterised by the presence of the so-called Sezary cell in the peripheral blood, the lymph nodes and the skin.

Histopathology: The histological features of MF are prototypical and correlate with the different clinical lesions. *Patch stage*: The diagnostic architectural hallmarks consist in the so-called string of pearls (at least four T-lymphocytes contiguously aligned within the basal layer), associated with Pautrier microabscesses (collection of at least four atypical T cells within the epidermis and papillary dermal fibrosis, with coarse horizontally disposed wiry bundles of collagen). MF cells (Lutzner cells) are lymphocytes of medium-large size (approximately the diameter of a basal keratinocyte nucleoli), with irregular convoluted nuclei (cerebriform nuclei) (Fig. 9.1a and b). These epidermotropic T cells are larger than those present in the papillary dermis and show a discrete halo. Often in Pautrier microabscesses they are intermingled with dendritic Langerhans cells. Absence or little spongiosis is mandatory. A clinico-pathological algorithm has been published [10] reporting different parameters to make diagnosis most reproducible. *Plaques stages*: The neoplastic cells represent the main contributor to dermal infiltrate unlikely patch stage. Epidermotropism is prominent sometimes associated with syringotropism and Pautrier microabscesses most frequent (Fig. 9.2). The tumour cells are highly atypical and form a dense band-like infiltrate within the papillary dermis and perivascular aggregates in the middle dermis. *Tumour stage*: A pan-dermal dense neoplastic infiltrate is typical of this stage with extension to the subcutaneous fat and possible sparing of the epidermis. *Large-cell transformation*: It is defined by the presence of more than 25 % large neoplastic cells forming clusters.

Immunophenotype: MF cell typically expresses CD2, CD3, CD4 and CD5. The diagnosis of MF is most challenging for the pathologist in the early stages because most dermal lymphocytes are reactive. Plenty of studies have tried to determine reproducible cut-offs of the CD8-/CD3-positive

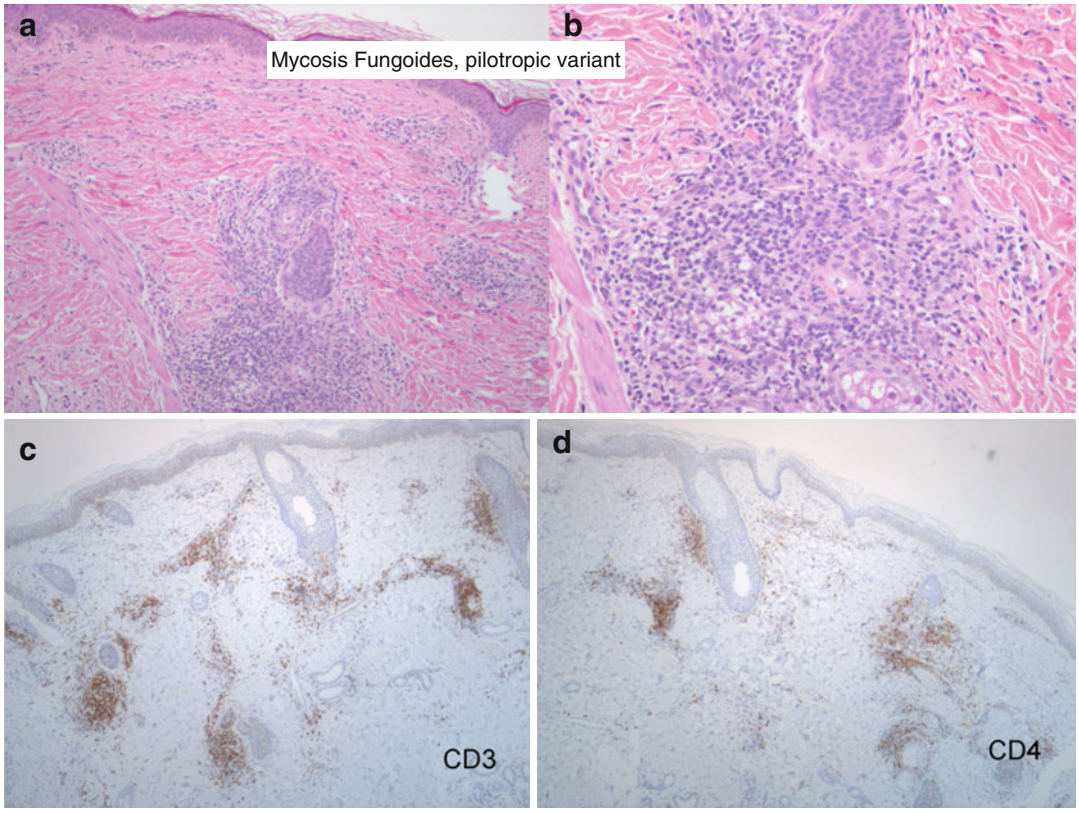

Fig. 9.2 Mycosis fungoides, pilotropic variant. (**a**, **b**) Morphologic detail of the relationship between the lymphoid infiltrate ad the pilo-sebaceous unit. (**c**, **d**) The lymphoid cells express the CD3 and CD4 antigen

cells in order to help discriminating early MF from reactive dermatoses. Assessing of CD4 cells has been avoided because of cross-reaction with histiocyte population. Different studies show that CD8/CD3 is significantly lower in MF when compared with controls, and other reports suggest that CD4/CD8 more than 2 is specific for MF. Actually semiquantification of lymphocyte subsets is unlikely to be routinely used. On the contrary, of more importance is the detection of T-cell-associated antigen loss, with special regards to CD7 and at less extent CD5 downregulation. The suggested immunohistochemical baseline includes a pan-B-cell marker (CD79a). With disease progression CD30 expression may be detectable in the large-cell component. Neoplastic cells of erythrodermic MF and SS share the same immune signature, but CD7 antigen loss is less frequent in the latter entity. Moreover, large cells in SS are often MUM1 positive.

Genetics: T-cell receptor genes are clonally rearranged in most of the cases of MF in plaques or tumour stage, while only about 50 % of the patch stages do not show any TCR gene rearrangement. Complex karyotypes are present in tumour stages of the disorders with many structural and numerical alterations described.

Primary Cutaneous CD30-Positive Lymphoproliferative Disorders

CD30 T-cell lymphoproliferative disorders comprise a spectrum of conditions ranging from lymphomatoid papulosis (Lyp) to anaplastic large-cell lymphoma (ALCL) and including borderline cases [21]. This group accounts for 30 % approximately of cutaneous T-cell lymphomas and has to be distinguished by cases of transformed

mycosis fungoides expressing CD30 antigen (a member of the tumour necrosis factor receptor family).

Extensive CD30 expression by the neoplastic population is mandatory for diagnosis of these entities which share a common pathogenetic pathway strictly involving the role of CD30/CD30L in activation of TRF2 (TNF receptor-associated factor) up to NF-kB signal transduction leading either to proliferation of apoptosis.

Owing to this mechanism, these lymphoproliferative disorders run a more favourable course and are amenable of regression. Most probably, past diagnosis of "regressing atypical histiocytosis" and "cutaneous Hodgkin disease" would be nowadays renamed as PC CD30 LPD.

It is of the utmost relevance to keep in mind that CD30-positive lymphocytes isolated or in clusters can be observed in a variety of inflammatory skin conditions, such as viral infections, arthropod bite reactions, lymphomatoid drug reaction and lupus pernio [22].

Lymphomatoid Papulosis (Lyp)

Clinical features: Red papules and nodules smaller than 1.5–2 cm or pink papulo-nodules, single or in clusters, predominantly affecting the trunk and limbs mostly of adults but even of children. The lesion may ulcerate in the centre and result in a scar. A waxing and waning course of the eruption is typical with tendency to spontaneous involution in 3–4 months and subsequent recurrences. The incidence of concurrent lymphoma or progression to lymphoma ranges between 4 and 20 % confirming the benign clinical course of this disorder. Yet, other malignant skin lymphomas, in particular mycosis fungoides, anaplastic large-cell lymphoma and Hodgkin lymphoma, may precede or follow Lyp.

Histopathology: Three main histologic subtypes have been described, with features merging one in the other and varying in relation to the age of the biopsied lesion.

Type A Lyp presents as a bottom-heavy striking polymorphous infiltrate with a distinct perivascular, perineural and eccrinotropic pattern, composed of small reactive lymphocytes, histiocytes and rare Sternberg-like atypical cells. An epidermal reaction with neutrophilic exocytosis and even necrosis and ulceration sustained by heavy vasculitis is frequent. Sometimes a granulomatous component with eosinophilia is evident so mimicking arthropod bite reaction. In *type B* Lyp, which is the less frequent variant, the infiltrate is still mixed, but large atypical cells begin to dominate and show a lichenoid distribution, resembling the plaque stage of mycosis fungoides. *Type C* Lyp lesions are featured by monotonous infiltrates of the large atypical cells and few small lymphocytes intermingled.

Immunophenotype: The large atypical cells of types A and C are CD30 positive and usually CD4+, so sharing the same signature of ALCL. In contrast, the large cells of Lyp B do not express CD30. Markers pointing to natural killer differentiation are generally negative, while cytotoxic antigen can be variably expressed.

A rare CD8+ form of Lyp has been described, histologically characterised by a granulomatous eccrinotropic infiltrate.

Genetics: t(2;5) translocation responsible of the protein ALK (anaplastic lymphoma kinase) has been occasionally reported. On the contrary T-cell gene rearrangement has been described in up to 60–70 % cases of Lyp.

Cutaneous Anaplastic Large-Cell Lymphoma

Clinical features: Usually single, but sometimes multiple, persistent large often ulcerative nodule, which does not undergo spontaneous regression. A cut-off of 2 cm in diameter has been proposed by some investigators to distinguish from Lyp. The median age of presentation is 60 years. A type C Lyp/borderline CD30-positive lymphoproliferative disease has been described, usually associated with a history of Lyp either concurrent or prior.

Secondary skin involvement of primary nodal ALCL, occurrence of ALCL in the setting of other lymphomas (mycosis fungoides and Hodgkin lymphoma) and ALCL in the context of

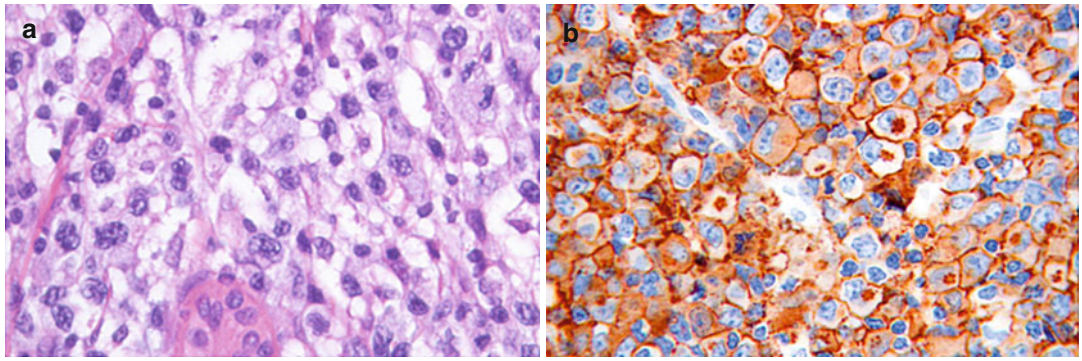

Fig. 9.3 Cutaneous anaplastic large-cell lymphoma. (**a**) Large pleomorphic cells, growing in a diffuse sheet-like pattern. (**b**) The neoplastic cells strongly express the CD30 antigen

post-transplant T-cell lymphoproliferative disorders represent other categories of this disease.

Histopathology: The common pattern shows a cohesive sheet-like growth, extending to the subcutis, of large cells, even multinucleated, with eccentric horseshoe-shaped nucleus and prominent eosinophilic Golgi region (Fig. 9.3). A small-cell variant exists with scattered atypical hallmark cells intermingled with dominant small-intermediate-sized atypical lymphocytes. Angiocentricity and angiodestruction by the neoplastic cells are frequent findings. Epidermotropism is reported. The epitheliomorphic feature of the cells can represent a challenging problem of differential diagnosis on morphological grounds with undifferentiated carcinoma. Other histological subtypes are the sarcomatoid, giant, neutrophilic-rich and histiocyte-rich variants. Mixed patterns are frequent. Histological variant does not influence prognosis with the exception of small-cell subtype, which runs a worse clinical course.

Immunophenotype: Immunohistochemical analysis shows a T-helper cell phenotype (CD3+, CD4+) of most cases, with a consistently positive CD30 staining and loss of pan-T-cell antigens. A null phenotype is not infrequent. EMA and ALK-1 are constantly negative in true primary ALCL of the skin. Clusterin a ubiquitous highly glycosylated protein, commonly positive in nodal ALCL, is variably detectable in the primary cutaneous disorder and cannot be used to distinguish the two entities. Nevertheless its cytoplasmic dot-like expression is typical of ALCL only and can be useful in the differential diagnosis with other T-cell malignancies. In the small-cell variant, the small lymphoid cells are typically negative.

Genetics: The majority of cases display clonal T-cell rearrangement. The (2;5)(p23;q35) translocation and its variants are rarely present in primary cutaneous ALCL, contrarily to the nodal counterpart.

Blastic NK-Cell Lymphomas

T-NK cutaneous lymphomas are a heterogeneous group of rare disorders, featured by overlapping immunophenotypical signature and morphology between T-cell lineage and NK cells.

The two main entities are extranodal NK/T cell of nasal type and blastic plasmocytoid dendritic cell neoplasm.

This last entity is a rare and intriguing disease affecting middle-aged patients, with aggressive biological behaviour and poor outcome due to massive bone marrow involvement and leukemic progression. The neoplastic growth shows the following immunophenotypic profile: CD43+, CD101+, CD123+ and TCL1+. Variable expression of CD68, TdT, BDCA-2, TIA1 and CD34 has been reported. The normal counterpart is the plasmocytoid dendritic cell precursor, possibly strictly related to a common myeloid/NK precursor cell.

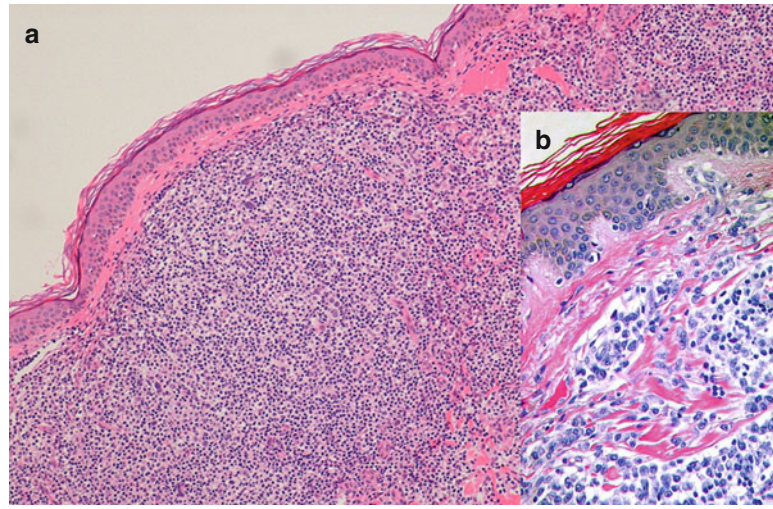

Fig. 9.4 Cutaneous marginal zone B-cell lymphoma. (**a**) Polymorphic lymphoid proliferation with bland cytologic atypia. (**b**) Peripheral plasma cellular components

Mature B-Cell Neoplasms

Cutaneous B-cell lymphomas (CBCL) account for approximately 20–25 % of all primary cutaneous lymphomas and probably occur far more frequently than is generally believed. They share an overall favourable prognosis and their proper identification is important to avoid overtreatment. The most relevant prognostic factors are histological type and size of the lesions.

Cutaneous Marginal Zone B-Cell Lymphoma (MALT Type)

Clinical features: Cutaneous marginal zone B-cell lymphoma (CMZL) affects patients in the fifth to sixth decades, with a male predominance, and may present with single or multiple red to violaceous papules, plaques and nodules involving the upper extremities or the trunk. Skin recurrences are frequent. In endemic areas *Borrelia burgdorferi* appears to be causal agent in some cases.

Histopathology: The pattern of growth may be perivascular, nodular or diffuse, involving the dermis and extending to the subcutis without epidermal infiltration (Fig. 9.4). Tumour cells surround and colonise reactive germinal centre and are composed of variable number of marginal zone B cells, with centrocyte-like or monocytoid morphology, mixed with plasma cells characteristically arranged at the periphery of the lymphoid nodules and subepidermally, together with scattered transformed B cell (sometimes more than 20 %). Plasma cell differentiation may be prominent. Intranuclear Dutcher bodies are commonly found. The presence of very immature plasma cells points to a possible secondary cutaneous involvement. Aggregates of CD123 dendritic plasmocytoid cells can be observed. Lymphoepithelial lesions are occasionally evident in eccrine ducts or secretory coils.

Immunophenotype: The marginal zone cells display a CD20+, bcl-2+, CD43+/−, CD10−, bcl-6−, CD5−, ciclina D1- and CD23 – phenotype. CD10 and bcl-6 are particularly useful in the differential diagnosis with primary follicle centre cell lymphoma. Light chain restriction of the lymphoplasmacytoid and plasma cells is detected in at least 80 % of the cases.

Genetics: IgH genes are clonally rearranged in more than 80 % of cases. t(14;18)(q32;q31) involving IgH and MALT1 genes is reported in about 30 % of cases. FAS gene mutation is present in a minority of cases. Recent studies [23] support the existence of a subset of CMZL characterised by monocytic plasma cells with class switch heavy chain expression and prominent mast cell component.

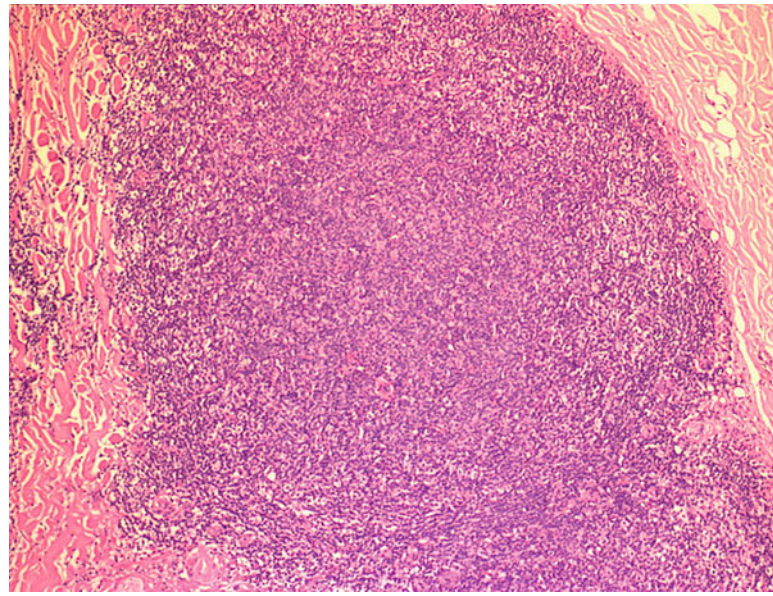

Fig. 9.5 Cutaneous follicle centre lymphoma: monomorphic neoplastic nodule, lacking a mantle zone and "tingible bodies" macrophages

Cutaneous Follicle Centre Lymphoma

Clinical features: Cutaneous follicle centre lymphoma (CFCL) manifests mainly in middle-aged adults, with no gender predominance, and represents the most common subtype of PCL. The presentation consists of firm erythematous plaques, nodules or tumours distributed on the trunk and/or head and neck districts. The previous term "Crosti lymphoma" or "reticulohistiocytoma of the dorsum" refers to a distinctive clinical presentation of this entity.

Histopathology: The infiltrate is composed of mature B cells of germinal centre derivation (centrocytes and centroblasts in variable proportion), arranged in superficial perivascular and deeper nodular or diffuse pattern of growth. The neoplastic follicles lack mantle zone, polarisation of the germinal centre and tangible bodies macrophages (Figs. 9.5 and 9.6). The proportion of large cells and the presence of a diffuse pattern of growth do not influence the prognosis (Figs. 9.7 and 9.8). A morphological spindle cell variant has been described which may be confused with a mesenchymal neoplasm (Fig. 9.9).

Immunophenotype: Neoplastic cells show positivity for B-cell markers (CD19, CD20, CD22) and bcl-6 protein, with CD10 variably expressed. On the contrary, bcl-6 expression is always maintained even in diffuse growth. In contrast to nodal follicular lymphomas, Bcl-2 is rarely demonstrated or faintly positive in the neoplastic follicles. A strong expression of CD10 and bcl-2 should address to a possible secondary nodal follicular lymphoma. The proliferation rate measured with the ki-67 index is typically low in the neoplastic proliferation. The presence of a network of CD21- and CD23-positive follicular dendritic cells helps in the differential diagnosis with CMZL. The presence of bcl-6 +/CD10+ centrocytes in the interfollicular region may help to define the neoplastic nature of the follicular infiltrate.

Genetics: Clonal IgH gene rearrangement is demonstrable in 90 % of the cases. On the contrary, t(14;18)(IgH;Bcl-2) is rarely shown by PCR but can be documented in up to 40 % by FISH analysis in those cases characterised by follicular pattern.

Primary Cutaneous Diffuse Large B-Cell Lymphoma

The WHO/EORTC classification scheme distinguishes primary cutaneous diffuse large B-cell lymphoma (PCDLBCL) leg type and other NOS type. The differential diagnosis of PCDLBCL is

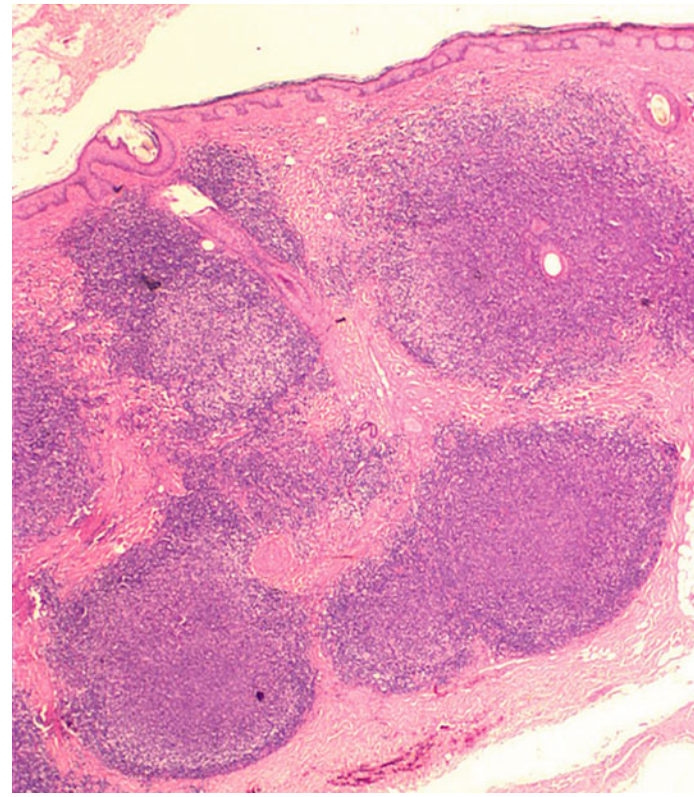

Fig. 9.6 Cutaneous follicle centre lymphoma: nodular lymphoid proliferation with sparing "grenz zone" and deep extension

broad and difficult to define histologically, because it encompasses histo-morphological spectrum of lymphoproliferative diseases and other malignant neoplasms mimicking lymphomas. The recognition of different histotypes of PCDLBCL has been an important advancement in the management of the patients because of variations in the biological behaviour of different entities. Indeed prognosis of PBDLBCL variably depends on specific factors both clinical (anatomic site and extent of the disease) and immunological (immunophenotype). Patients who present with solitary or few lesions have a much better prognosis than those with multiple lesions.

Primary Cutaneous Diffuse Large B-Cell Lymphoma: Leg Type

Clinical features: PCDLBCL leg type is the most common form of PCDLBCL and accounts for 5–10 % of all cutaneous B-cell lymphomas. It

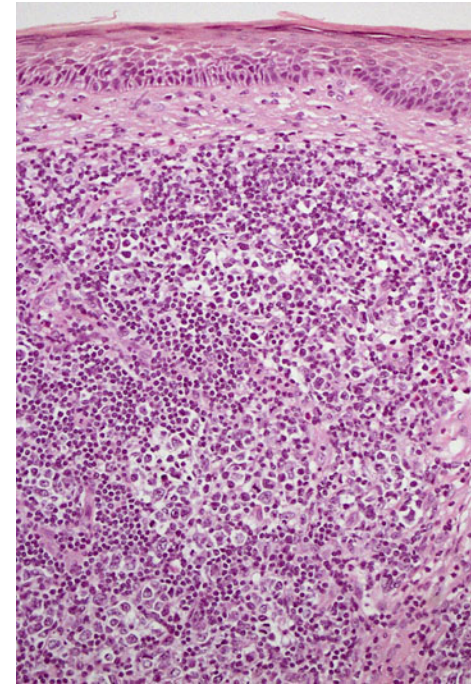

Fig. 9.7 Cutaneous follicle centre lymphoma: centroblasts predominate in the neoplastic nodule

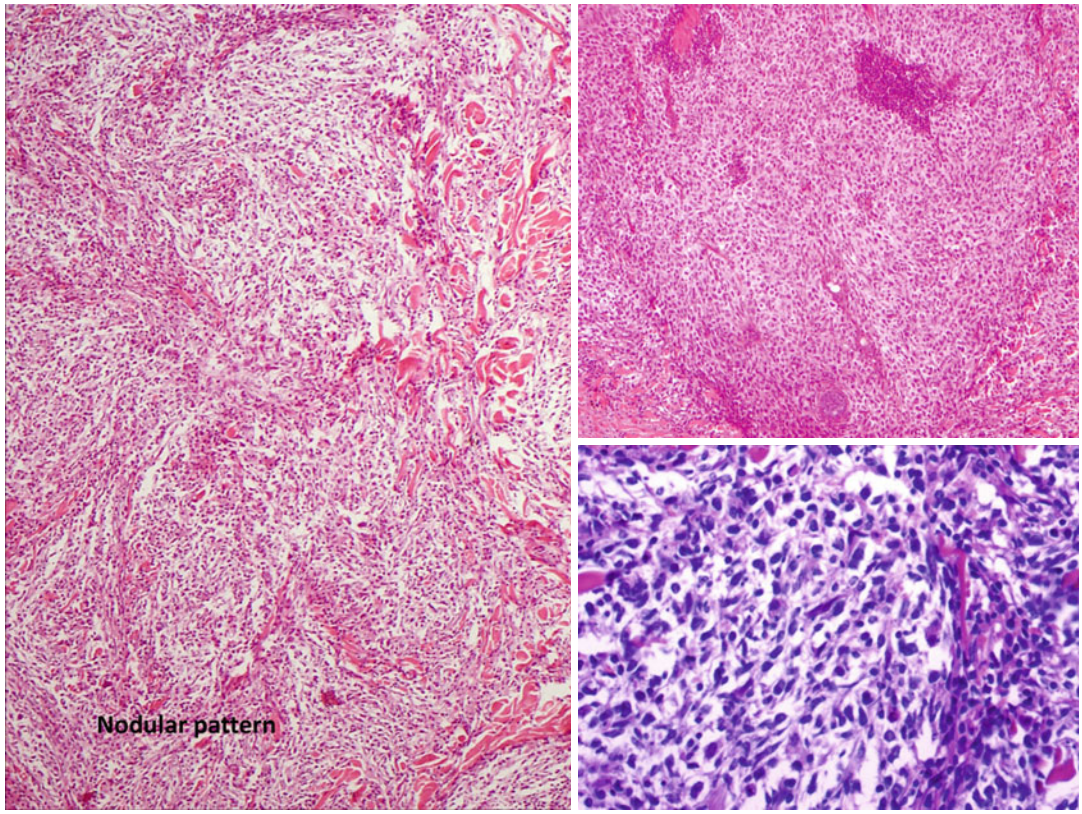

Fig. 9.8 Cutaneous follicle centre lymphoma, spindle cell variant: nodular pattern of the neoplastic growth

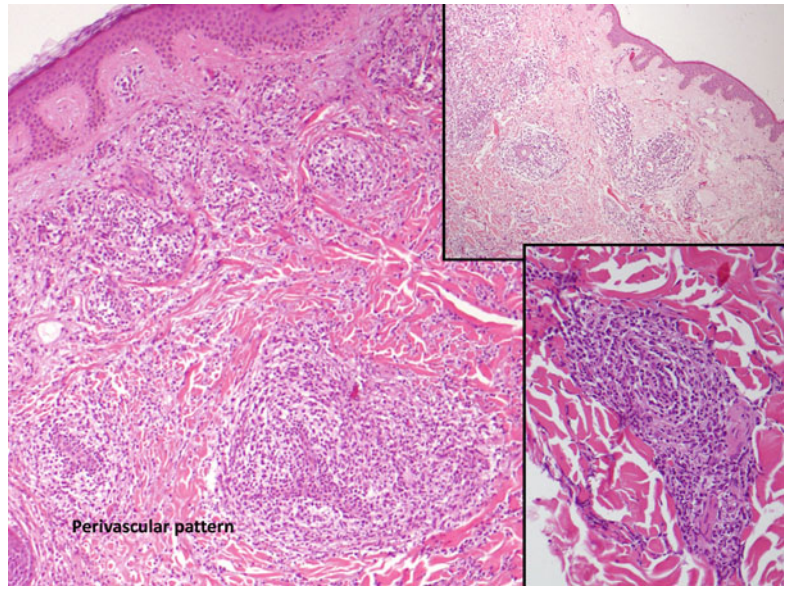

Fig. 9.9 Cutaneous follicle centre lymphoma, spindle cell variant: perivascular pattern of the neoplastic growth

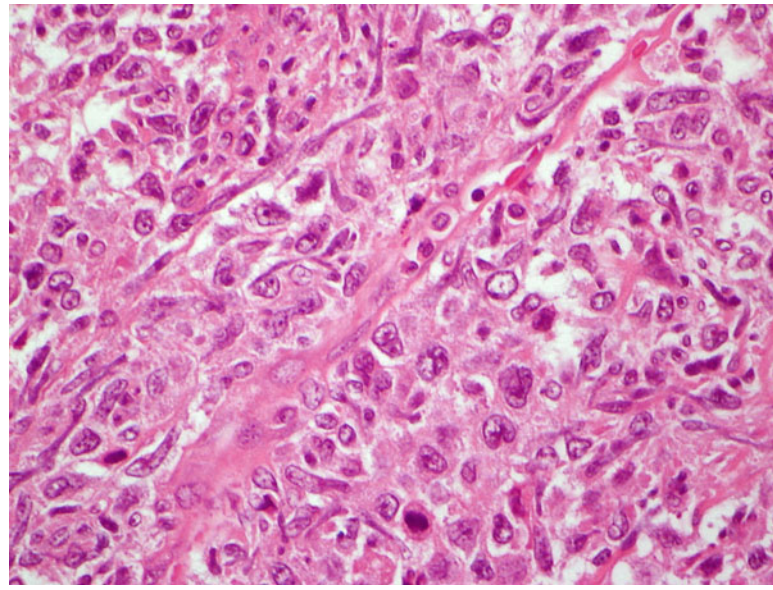

Fig. 9.10 Primary cutaneous diffuse large B-cell lymphoma – other type (NOS): the large-cell component is composed predominantly of centroblasts

frequently develops on the legs of elderly patients presenting with red nodules or plaques sometimes ulcerated, solitary or multiple. It exhibits an unfavourable prognosis, with frequent relapses and systemic dissemination. A minority of cases are recognised on non-leg sites.

Histopathology: The infiltrate is composed predominantly of centroblast- and immunoblast-like tumour cells, with round non-cleaved nuclei and prominent nucleoli, with brisk mitotic activity and numerous apoptotic cells (Fig. 9.10). Epidermotropism is unusual and proliferation involves mainly the dermis with a diffuse pattern.

Immunophenotype: The neoplastic B cells express pan-B-cell markers (CD20, CD79a) and are nearly always strongly positive for bcl-2, IRF4/MUM1 and FOXP1. Bcl-6 stains positively in most cases, while CD10 is usually negative.

Genetics: Clonality studies show clonal rearrangement of IgH genes. FISH analysis frequently shows translocations involving C-MYC, BCL-6 and IgH genes. T(14;18) is not found in this lymphoma, and the marked BCL-2 positivity by immunohistochemistry may be explained by amplification of the BCL-2 gene.

Primary Cutaneous Diffuse Large B-Cell Lymphoma: Other Type (NOS)

This category is very heterogeneous comprising morphological variants, which in most cases represent cutaneous involvement by systemic diseases, with special regard to intravascular large B-cell lymphoma, T-cell-rich large B-cell lymphoma and plasmablastic diffuse large B-cell lymphoma [24].

Intravascular Large B-Cell Lymphoma

Clinical features: Intravascular large B-cell lymphoma (ILBCL) is an aggressive and usually disseminated disease typically affecting elderly patients. Patients with involvement limited to the skin (so-called cutaneous variant) show a better outcome than those who present multiorgan involvement. Cutaneous presentation is polymorphous, including painful telangectatic lesions, panniculitis, erythematous streaks, plaques and tender nodules.

Histopathology: The large neoplastic lymphoid cells are trapped in vascular lumina within the dermis and the subcutis, making deep biopsies

mandatory for diagnostic purposes. Mitotic index is constantly high.

Immunophenotype: Tumour cells beyond positivity for pan-B-cell markers may co-express CD10 and CD5. Overexpression of bcl-2 is not accompanied by BCL2 gene rearrangement.

Genetics: Immunoglobulin genes are clonally rearranged.

Glossary

Epidermotropism Tendency to infiltrate the epidermis

Extranodal A localisation of lymphoproliferative neoplasms different from a lymph node

Grenz zone An area savings the epidermis

Mono(poly)clonality Belonging to a single (or multiple) cell clone(s)

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