CHAPTER 4

Haematolymphoid Tumours

Lymphoma may involve the skin as the primary and only site of involvement, or may spread to the skin as a secondary site of disease. Some cutaneous lymphomas morphologically resemble their counterparts in lymph node, but differ in terms of phenotype, genotype, and clinical behaviour, suggesting that they represent an independent entity. Cutaneous follicular lymphoma demonstrates such fundamental differences from nodal follicular lymphoma. Some lymphomas present only in the skin, but never primarily in lymph nodes or other extranodal sites. Mycosis fungoides is one such example. Finally, some cutaneous lymphomas exhibit a different clinical behaviour from their nodal counterparts, despite apparent phenotypic and genotypic similarities.

The members of the WHO Working Group, together with their colleagues from EORTC, were able to formulate a classification that respects the many unique features of skin lymphomas but avoids a terminology restricted to primary cutaneous lymphomas. We are confident that this proposal will be used by pathologists and dermatologists world-wide for years to come.
### WHO / EORTC classification of cutaneous lymphomas

**Mature T-cell and NK-cell neoplasms**

<table>
<thead>
<tr>
<th>Category</th>
<th>Code</th>
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</thead>
<tbody>
<tr>
<td>Mycosis fungoides</td>
<td>9700/3</td>
</tr>
<tr>
<td>Pagetoid reticulosis (localized disease)</td>
<td>9700/3</td>
</tr>
<tr>
<td>Follicular, syringotropic, granulomatous variants</td>
<td>9700/3</td>
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<tr>
<td>Granulomatous slack skin</td>
<td>9700/3</td>
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<tr>
<td>Sézary syndrome</td>
<td>9701/3</td>
</tr>
<tr>
<td>CD30+ T-cell lymphoproliferative disorders of the skin</td>
<td>9718/1</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>9718/3</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large cell lymphoma</td>
<td>9718/3</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma**</td>
<td>9708/3</td>
</tr>
<tr>
<td>Primary cutaneous peripheral T-cell lymphoma (PTL), unspecified</td>
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</tr>
</tbody>
</table>

**Subtypes of PTL (provisional)**

- Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma
- Cutaneous gamma/delta-positive T-cell lymphoma
- Primary cutaneous small/medium CD4+ T-cell lymphoma
- Extralymphatic NK/T-cell lymphoma, nasal type
- Hydroa vacciniforma-like lymphoma (variant)
- Adult T-cell leukaemia/lymphoma* 9827/3
- Angioimmunoblastic T-cell lymphoma* 9705/3

**Mature B-Cell neoplasms**

<table>
<thead>
<tr>
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<tr>
<td>Cutaneous marginal zone B-cell lymphoma (MALT-type)</td>
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<tr>
<td>Cutaneous follicle centre lymphoma</td>
<td>9690/3</td>
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<tr>
<td>Cutaneous diffuse large B-cell lymphoma</td>
<td>9680/3</td>
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<td>Intravascular large B-cell lymphoma*</td>
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<tr>
<td>Lymphomatoid granulomatosis*</td>
<td>9766/1</td>
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<tr>
<td>Chronic lymphocytic leukaemia*</td>
<td>9823/3</td>
</tr>
<tr>
<td>Mantle cell lymphoma*</td>
<td>9673/3</td>
</tr>
<tr>
<td>Burkitt lymphoma*</td>
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**Imature haematopoietic malignancies**

<table>
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<tr>
<th>Category</th>
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<tr>
<td>Blastic NK-cell lymphoma ***</td>
<td>9727/3</td>
</tr>
<tr>
<td>CD4+/CD56+ haematodermic neoplasm</td>
<td>9727/3</td>
</tr>
<tr>
<td>Precursor lymphoblastic leukaemia/lymphoma</td>
<td>9837/3</td>
</tr>
<tr>
<td>T-lymphoblastic leukaemia*</td>
<td>9837/3</td>
</tr>
<tr>
<td>T-lymphoblastic lymphoma*</td>
<td>9729/3</td>
</tr>
<tr>
<td>B-lymphoblastic leukaemia*</td>
<td>9836/3</td>
</tr>
<tr>
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**Myeloid and monocytic leukaemias***

<table>
<thead>
<tr>
<th>Category</th>
<th>Code</th>
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</thead>
<tbody>
<tr>
<td>Hodgkin lymphoma*</td>
<td>166</td>
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</tbody>
</table>

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1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (786) and the Systematized Nomenclature of Medicine (http://snomed.org).
2. Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
3. Extracutaneous lymphomas frequently involving the skin as a secondary site are printed in italics.
4. Definition is restricted to lymphomas of alpha/beta T-cell origin.
5. Recent evidence suggests an origin from a dendritic cell precursor. In recognition of uncertain histogenesis, the term CD4+/CD56+ haematodermic neoplasm is preferred.
<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>Ia</td>
<td>T1 Limited lesions covering &lt;10% of the skin surface</td>
<td>N0 no palpable lymph nodes, pathology negative for CTCL</td>
<td>M 0 no involvement of visceral organs</td>
</tr>
<tr>
<td>Ib</td>
<td>T2 generalized lesions covering 10% and more of the skin surface</td>
<td>N0 no palpable lymph nodes, pathology negative for CTCL</td>
<td>N0 no involvement of visceral organs</td>
</tr>
<tr>
<td>IIa</td>
<td>T1 Limited lesions covering &lt;10% of the skin surface, or T2 generalized lesions covering 10% and more of the skin surface</td>
<td>N1 palpable peripheral lymph nodes, pathology negative for CTCL</td>
<td>M 0 no involvement of visceral organs</td>
</tr>
<tr>
<td>IIb</td>
<td>T3 tumours, one or more</td>
<td>N0: no palpable lymph nodes, pathology negative for CTCL or N1 palpable peripheral lymph nodes, pathology negative for CTCL</td>
<td>M 0 no involvement of visceral organs</td>
</tr>
<tr>
<td>III</td>
<td>T4 generalized erythroderma</td>
<td>N0: no palpable lymph nodes, pathology negative for CTCL or N1 palpable peripheral lymph nodes, pathology negative for CTCL</td>
<td>M 0 no involvement of visceral organs</td>
</tr>
<tr>
<td>IVa</td>
<td>T1-4</td>
<td>N2: no palpable peripheral lymph nodes, pathology positive for CTCL or N3: palpable peripheral lymph nodes, pathology positive for CTCL</td>
<td>M 0 no involvement of visceral organs</td>
</tr>
<tr>
<td>IVb</td>
<td>T1-4</td>
<td>N0-3</td>
<td>M 1 involvement of visceral organs</td>
</tr>
</tbody>
</table>

Modified, from Refs. (333,344,2537).
The skin is the second most common site of extranodal lymphoma, following the gastrointestinal tract (340). Lymphoma may involve the skin as the primary and only site of involvement, or may spread to the skin as a secondary site of disease. Because the clinical implications of primary and secondary cutaneous lymphoma are different, the dermatologist and pathologist should be familiar with both types of neoplasms. For this reason it also is problematic to use a classification system restricted to primary cutaneous lymphomas (2523). It is important for dermatologists, haematoooncologists, and pathologists to use a unified system for the diagnosis and treatment of cutaneous lymphoma (1858).

Nevertheless, cutaneous lymphomas present some unique clinical aspects. There are some diseases that present only in the skin, and are never primary in lymph nodes or other extranodal sites. Mycosis fungoides is one such example. Some cutaneous lymphomas morphologically resemble their counterparts in lymph node, but differ in terms of phenotypic, genotypic, and clinical behaviour, suggesting that they represent an independent entity. Cutaneous follicular lymphoma demonstrates such fundamental differences from nodal follicular lymphoma. Finally, some cutaneous lymphomas exhibit a different clinical behaviour from their nodal counterparts, despite apparent phenotypic and genotypic similarities. These differences may be related to stage or tumour burden, or more fundamental biological differences. For example, some lymphomas composed of large centrocytes and centroblasts have an indolent clinical course when presenting as a localized cutaneous tumour, but a similar cytological process in lymph node would be considered aggressive, i.e. diffuse large B-cell lymphoma. Dermatologists, haematoooncologists, and pathologists must use a common language. In this spirit we utilize the WHO classification of lymphoid neo-

plasms (1121), but we expand upon the unique features of many cutaneous lymphomas to emphasize their distinctive clinical and biological characteristics (336A,2522). Additional clinical and morphological variants have been added, where appropriate, in order to comprehensively cover the many manifestations of cutaneous lymphoma. Atypical reactive lesions that may represent precursors of cutaneous lymphoma are discussed where relevant (336A,2522).

**Cutaneous lymphoproliferative disorders (CLD)**

These include reactive lymphoid hyperplasias (so called cutaneous “pseudolymphomas”), prelymphomatous conditions and definite malignant lymphoma of low grade or of high grade malignancy. According to their biologic behaviour, CLD can be subgrouped into prognostic categories which are not reflected in the classifications, which however are of special interest for the patient and for the treating physician.

When diagnosing a cutaneous lymphoproliferative disorder, both the clinicopathologic classification and the biologic category should be considered. The advantage of such an approach is to provide the diagnosis according to the current WHO-classification of lymphomas, and in addition, to include essential information about the biologic behaviour, which may be significantly different than that of the nodal counterpart. These data are crucial for the clinician involved in counseling and treatment of the patient.

**Reactive lymphoid hyperplasias (RLH) (pseudolymphomas)**

These are reactive benign lymphoproliferative processes, localized or disseminated, which heal either spontaneously after elimination of the causative factor (e.g. drugs) or after treatment with non-aggressive (no severe side effects to be expected after long term application) modalities, and which do not recur after removal of the causative agent.

**Prelymphomatous (“abortive”) disorders (PLD)**

PLD show a chronic long-standing course, no spontaneous regression in most cases, and no extracutaneous spread with involvement of visceral organs. In some cases, clonality of the infiltrate can be demonstrated. However, in most cases the neoplastic cell clone never overcomes host control mechanisms and cannot expand and therefore does not convert into definite malignant lymphoma. Survival time is not affected. Definite malignant lymphoma of low-grade malignancy (LLM). This category includes cutaneous lymphomas that show a slowly progressive course with systemic spread in later stages and have the potential for transformation into more aggressive high-grade malignant lymphomas. Survival time usually is greater than 5 years.

**Definite malignant lymphoma of high-grade malignancy (LHM)**

These diseases are characterized by a more rapid course than the low-grade lymphomas and usually exhibit a bad prognosis with survival times less than 5 years.
Mycosis fungoides

Definition
Mycosis fungoides (MF) is the prototype of cutaneous T-cell lymphomas (CTCL) and can be defined as a peripheral, epidermotropic non-Hodgkin T-cell lymphoma of low grade malignancy initially presenting in the skin and showing step-wise clinical progression from patches to plaques and tumours, and distinct histological (except in early stages), phenotypic and genotypic features.

ICD-O code 9700/3

Synonyms and historical annotation
In 1806 Jean-Louis Alibert (1768-1837) presented an extraordinary skin disease which he described in detail under the name of "Pian fungoides" in 1814 and as "Mycosis fungoides" in 1832 (58). At his time the etiology of the disease was completely unclear. It is worth noting that Alibert in 1832 copied part of the text from Bontius (283). Ernest Bazin (1807-1878) published three different stages (184): Période érythematuse (erythematous stage: red colored patches) Période lichénoid (the lichenoid stage: itching and different plaques with small papules). Période fongoïdique, mycositique (fungal stage: mushroom-like tumours of different size).

Epidemiology
The incidence of MF from 1973 through 1992 in the USA was 0.36/ 100'000 persons per year (2445). Most frequently MF affects adults, usually in their 5th-6th decade, with a male to female ratio of approximately 2:1 and a preponderance of black (1.7) vs white populations.

The increase of frequency paralleled by a decrease of mortality rates between 1979 and 1991 (2485) most probably is due to changing criteria resulting in over-diagnosing MF by including non-neoplastic conditions into this group. Data collected by the Surveillance, Epidemiology and End Results Program (SEER) of the US National Cancer Institute indicate that the relative survival changed little after 11 years, at which point it was 66% (2485).

Etiology
The etiology of MF is unknown. The role of environmental antigens, viruses or bacteria is controversial (2605).

Localization
All parts of the skin may be involved without any predilection site.

Clinical features
Clinically MF is characterised by a step-wise evolution with sequential appearance of patches, plaques and tumours. Patches are circumscribed lesions with discolouration and sometimes little scaling, without palpable infiltration of the skin. Plaques usually evolve out of patches and present with palpable infiltration of various degree (thin and thick plaques). Tumours exhibit an exophytic growth in most of the cases and tend to ulcerate. In advanced stages of the disease there may be spread into the peripheral blood, involvement of lymph nodes, bone marrow and internal organs. Besides physical examination, including mapping of skin lesions and photodocumentation, a skin biopsy for paraffin embedding and for cryo-preservation should be taken, preferentially at multiple sites. Additional investigations include blood cell counts with PAS staining for Sézary cells, chest x-ray and CT-scan of abdomen and of peripheral lymph nodes. There is no need for taking a bone marrow biopsy in early patch and plaque stages of MF without atypical cells in the peripheral blood. Biopsy of enlarged lymph nodes is mandatory.

Tumour spread and staging
MF, like other cutaneous lymphomas, is a systemic disease with preferential homing and proliferation of neoplastic lymphocytes into the skin. Therefore skin lesions may spread all over the body sur-

Fig. 4.1 Mycosis fungoides. A Large patches involving hip and abdomen. B Plaque-stage MF affecting the left arm. C Medium-sized hyperconvoluted cerebriform cells with prominent cytoplasmic halos in the epidermis, aligned within the basal layer.
face. Spread to extracutaneous compartments occurs in advanced stages of the disease, due to change or loss of homing receptors. These changes are usually accompanied by a change of cytology of the tumour cells from small cerebriform to medium-sized pleomorphic or large blast-like cells.

**Histopathology**

The histologic diagnosis of MF is based on numerous subtle changes, most of which may be present to some degree in many inflammatory and neoplastic cutaneous conditions. The most significant criteria, which however in early lesions often are missing or are only present in part, are Pautrier microabscesses, exocytosis of lymphocytes, disproportionate epidermotropism. The presence of cells with hyperconvoluted cerebriform nuclei in the epidermis larger than dermal lymphocytes, or lymphocytes in clusters in the dermis, and lymphocytes aligned within the basal layer without or with only little spongiosis and without prominent vacuolisation in the dermo-epidermal junction are typical but not specific features. Haloed lymphocytes have proved to be the most robust discriminator of MF from non-MF.

**Patch stage**

The diagnosis is usually based on a combination of specific histologic criteria, without the necessity of confirmatory immunophenotyping (2058;2059,2213). Wherein in very early “prelymphomatous” patch stages the histological picture often is non-specific, the histological findings become diagnostic in the thin plaque stage, when a denser infiltrate with lymphocytes lining up in the basal layer, especially at the tips of the rete ridges with epidermotropism of single cells is present. The majority of cells are small, differentiated lymphocytes with round or only slightly cerebriform nuclei. Haloed cells may predominate in the epidermis in early patch lesions of patients with otherwise advanced disease. In addition, there can be mild acanthosis, hyperkeratosis, signs of basal layer damage (pigment incontinence), edema or fibrosis of the papillary dermis. There is proliferation of postcapillary venules with prominent endothelial cells, simulating giant cells. The infiltrate may contain an admixture of eosinophils, plasma cells, macrophages, and dermal dendritic cells (922,2156).

**Thick plaque stage**

This is typified by a dense, subepidermal, usually band-like infiltrate containing a high number of cerebriform cells. Epidermotropism is more prominent with small intraepidermal clusters (2-3 cells) of lymphocytes. Typical Pautrier microabscesses are seen only in approximately one-third of cases. Subcorneal, intrapapillary and subepidermal bullous formation may result from confluence of Pautrier microabscesses (1460).

**Progression to tumour stage**

With progression from plaque stage to tumour stage the dermal infiltrates become more diffuse, and epidermotropism may be lost. The proportion of tumour cells increase both in number and size, and may include cells with small, medium-sized and large cerebriform nuclei, blast cells with prominent nuclei and intermediate forms. There is a concomitant decrease in the numbers of reactive T-cells and dendritic cells. In approximately 25% of advanced cases, transformation to a CD30 positive or negative large T-cell lymphoma defined by
the presence of more than 25% blast cells may be observed.

**Immunoprofile**

The immunophenotypical prototype of MF is CD2+, CD3+, CD4+, CD5+, CD45RO+, CD8, TCR-beta+, CD30-. During progression of the disease loss of CD7, 2 and 5 can occur. Helpful in the diagnosis is the loss of CD7, CD2, CD5, or CD4 in the epidermotropic cerebriform cells. During progression of the disease especially when transformation is present CD4 positive epidermotropic cells can have a cytotoxic phenotype (TIA-1, Granzyme B). In the transformed stage the blast cells can express CD30. Besides the CD4 prototype, a small number of MF cases have a CD8 positive cytotoxic phenotype (TIA-1 and granzyme B). These cases have the same clinical behaviour as the CD4 positive cases.

**Prelymphomatous precursor lesions**

The term “parapsoriasis” is confusing and requires explanation. It encompas-ses a number of different pathologic states clinically manifested by chronic recalcitrant erythematous scaling lesions (311, 312, 1375).

Two groups of parapsoriasis can be differentiated (337). The benign form ‘parapsoriasis en plaques’ (Brocq disease), never evolve into malignant lymphoma. The large plaque forms (LPP) with poikiloderma (prereticulotic poikiloderma, parapsoriasis en grandes plaques poikilodermiques, poikiloderma vasculare atrophicans, parapsoriasis lichenoides, parakeratosis variegata) or without poikiloderma (parapsoriasis en plaques, premalignant type, parapsoriasis en grandes plaques simples), may after several decades evolve into mycosis fungoides or CTCL in up to 10-50% of cases. Few large (more than 5 cm in diameter) patches show pityriasisiform scaling with (poikilodermatous variant) or without telangiectasia and netlike pigmentation. There is no palpable infiltration. Histologically lesions in large plaque parapsoriasis (LPP) are different from MF or other CTCL. Under patchy parakeratosis there is slight atrophy of the epidermis, due to loss of rete ridges. The subepidermal zone is free of lymphocytes, which accumulate in a band-like arrangement in the upper dermis, spar-

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**Fig. 4.4 Tumour-stage mycosis fungoides (MF).** 


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**Fig. 4.5 Histopathology of transformed mycosis fungoides (MF).** 

A Large-cell pleomorphic transformation. B Large cell anaplastic transformation. C Immunohistochemistry reveals CD30 positive tumour-cells.
Somatic genetics
There have been a few reports on familial occurrence of MF or CTCL {2160} and on a possible association of HLA-DR5 with MF {2004}. HLA class II susceptibility alleles, i.e. HLA-DRB1*11, HLA-DQB1*03 and HLA-DRB1*1104 are more prevalent among patients with MF and are likely to be important in the pathogenesis of MF {1039,1118}. T-cell receptor beta and gamma chain genes are clonally rearranged. In advanced cases with extracutaneous involvement, the same clone is usually detected in the skin and in the extracutaneous lesions. In transformed cases the same clone is present in the pre-existing lesions and the high-grade lymphoma {207}.

In advanced stage, the rate of chromosomal aberrations, especially of chromosomes 1, 6 and 11, increase with the activity of the disease and has prognostic significance in patients with MF. Aberrations of chromosomes 8 and 17 are especially associated with active or progressive disease.

Chromosomal abnormality possibly results in increased genetic instability as a basic prerequisite for the development of CTCL. In G-banding studies, numerical aberrations of chromosomes 6, 13, 15, and 17, marker chromosomes, and structural aberrations of chromosomes 3, 9, and 13 were increased in MF {1209}. In contrast to nodal lymphomas, the large cell transformation in cutaneous T-cell lymphoma (CTCL) is not associated with t(2;5)(p23;q35) chromosomal translocation {613,1420}.

Increased expression of C-myc, p62, TP53 and proliferation markers (PCNA) has been found in advanced stages of MF as compared to early stages of MF suggesting a relationship between levels of these proteins and aggressiveness of CTCL {1192}.

Prognosis and predictive factors
The majority of MF patients show an indolent clinical course over years or decades. The prognosis of the disease is defined by its stage. Patients with early
stages, i.e. with patches or thin plaques, without involvement of lymph nodes, peripheral blood or other extracutaneous compartment have an excellent prognosis with survival similar to that of an age, sex, and race-matched population (2575). Advanced stage and age above 60 years of age indicate a poor prognosis. When extracutaneous involvement or transformation into high-grade lymphoma occurs, expected survival is usually less than one year (2367,2412).

Variants
Apart from the classical form of MF, there are several variants of this disease with unusual or atypical clinical and/or histopathological features. These comprise follicular, bullous, dyshidrotic, granulomatous, hypopigmented, poikilodermic, hyperpigmented, pigmented purpura-like, unilesional, palmoplantar, hyperkeratotic/verrucous, vegetating/papillomatous, ichthyosiform, pustular and other forms (1234). Pagetoid reticulosis, syringotropic MF, folliculotropic (pilotropic) and granulomatous MF also are variants and deserve special emphasis.

Pagetoid reticulosis
Pagetoid reticulosis, in its localized form also referred to as Woringer-Kolopp disease (WKD) (302,2550) clinically presents as a solitary, slowly growing psoriasiform crusty or hyperkeratotic patch or plaque, typically on a distal limb. The histological hallmark is the sponge-like disaggregation of the epidermis by small to medium-sized lymphoid cells (pagetoid) which immunophenotypically correspond to those found in MF in most of the cases (336). However, the neoplastic cells in WKD often demonstrate a higher proliferation rate (>30%) in comparison to lymphocytes in patch or plaque stage MF (<10%), and in some cases infiltrates in WKD may contain high numbers of CD30+ cells (937). CD8+ (792) variants have also been reported. There exists a disseminated form featuring the same distinct pagetoid pattern of the infiltrate (1252), which is now regarded as a separate disease, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

Syringotropic MF
Syringotropic MF represents a rare variant of MF (2586) showing a solitary well circumscribed red-brown plaque with hair loss in the affected area. Histology reveals predominant involvement of irregularly proliferating eccrine sweat glands by small cerebriform lymphocytes (343,2586).

Folliculotropic MF
Follicular MF, also referred to as pilotropic MF (776) is a rare variant, histopathologically characterized by infiltrates of atypical T lymphocytes around and within the epithelium of the hair follicles with sparing of interfollicular skin. The follicles may show cystic dilatation and/or cornified plugging. There may or may not be mucinosis. When present, mucinous degeneration of the follicular epithelium varies from focal spots of mucin deposition to complete destruction of follicles with mucin lakes. The folliculotropism is
possibly due to an increased expression of skin-selective homing receptors and adhesion molecules in the follicular epithelium (1805). A recent study has demonstrated that follicular MF shows a more aggressive behaviour and a worse prognosis than classical MF (829,2411).

**Granulomatous MF**

Granulomatous MF is characterized by the histological presence of a granulomatous reaction (584), sometimes featuring a sarcoidal or granuloma annulare-like pattern. Multinucleated giant cells may be present (1387). The prognostic and clinical significance of a granulomatous reaction in MF remains uncertain (454).
Sézary syndrome

Definition
Sézary syndrome (SS) is a rare variant of cutaneous T-cell lymphoma (CTCL), characterized by erythroderma, blood involvement and a poor prognosis. Neoplastic lymphocytes are typically mature T-helper cells with cerebriform nuclei. Criteria for the diagnosis of SS include the demonstration of a peripheral blood T-cell clone by molecular or cytogenetic methods; an expanded CD4+ population resulting in a CD4:CD8 ratio > 10, and immunophenotypic abnormalities such as absent expression of T-cell antigens (CD2, CD3, CD4 and/or CD5). Sézary syndrome (SS) is part of a broader disease spectrum, erythrodermic CTCL. The presence of a clonal T-cell population in the peripheral blood distinguishes SS from reactive disorders that exhibit erythroderma and circulating cells with cerebriform nuclei (pseudo-SS) (777).

ICD-O code 9701 / 3

Epidemiology
Sézary syndrome accounts for less than 5% of all cutaneous T-cell lymphomas (2523). It occurs almost exclusively in adults, characteristically presents over the age of 60 and has a male predominance (2523).

Etiology
SS is of unknown etiology. However, a syndrome clinically indistinguishable from SS is occasionally seen in HTLV-1 associated lymphoma/leukaemia.

Clinical features
SS comprises a clinical triad of pruritus, erythroderma and lymphadenopathy. The pruritus is commonly intractable and sufficiently severe to prevent the patient sleeping or pursuing a normal life. Additional clinical features include alopecia, ectropion, nail dystrophy, palmoplantar keratoderma and leonine facies. Bacterial skin infection is common in Sézary patients and may lead to a marked deterioration in their cutaneous disease. An increased prevalence of secondary malignancies, both cutaneous and systemic, has been reported in SS and attributed to the immunoparesis associated with loss of normal circulating CD4 cells (2075).

Tumour spread and staging
Haematological involvement was defined in the TNM classification of MF as more than 5% atypical circulating lymphocytes (B1), but was not included as part of the Bunn-Lamberg staging system (1356). Sézary patients are all T4/B1 (erythroderma with blood involvement) but staging will vary from stage III if there is no lymph node involvement to IVB if there is bone marrow involvement. In practice, most cases of SS are staged as IVA. In 1988, the definition of B1 was increased from 5 to 20%, by the NCI, but was still not included as part of the staging system (2071).

The problem is that erythrodermic CTCL represents a spectrum and that any attempt to distinguish SS from cases that show a lesser degree of haematological involvement is necessarily arbitrary. An alternative approach is to develop a staging system that incorporates both lymph node status and haematological stage. A haematological staging system...
comprising five categories (H0-H4) was proposed by Russell-Jones and Whittaker (1998), and subsequent data showed an increase in disease-specific death rates for each category with the most significant change occurring at H2, defined by 5% Sézary cells with a T cell clone demonstrated by PCR, or a T cell clone demonstrated by Southern blot analysis only (2077). The need for a haematological staging system has also been recognised by the International Society for Cutaneous Lymphoma ISCL (2444). Currently this is being tested in a larger, multi-centre study under the auspices of the ISCL.

**Histopathology**

Despite minor differences (1099), the range of histological changes in SS are not dissimilar to those seen in patients with mycosis fungoides (2135). Epidermotropism is a variable feature, and the size of Sézary cells varies in the skin as it does in blood. Only 2/3 of the skin biopsies and 73% of patients had diagnostic changes in the skin biopsies. Other causes of erythroderma need to be differentiated from SS, particularly drug induced erythroderma and chronic actinic reticuloid, both of which may show a high proportion of activated lymphocytes with cerebriform nuclei (2135). In cases with a non-specific histology, the differential diagnosis would include other causes of erythroderma such as eczema or psoriasis.

**Immunoprofile**

A typical Sézary cell is a mature helper T cell with a memory phenotype. A classic immunoprofile is CD2, CD3, CD4, CD5, CD45RO positive and CD8 negative (1368, 2526). The majority of Sézary cells are also CLA positive (1827) and CD7 negative, and this latter feature has been proposed as a method of distinguishing Sézary cells from normal lymphocytes (957). However, further studies have shown that the neoplastic cell population is present in both the CD7 positive and CD7 negative subset in the same patient (657). More recently, Bernengo et al have demonstrated that CD4 positive Sézary cells typically loose the CD26 marker and that a diagnosis of SS or MF with haematological involvement can be made if the CD26 negative subset exceeds 30% of the CD4 positive cells (215).

Complete loss of T cell antigens such as CD2, CD3, CD4, or CD5 is present in approximately 2/3 of patients with SS (957). An alternative approach would be the identification of a tumour-specific antigen (669). Recently two differentiation antigens P140 and SCS have been reported in circulating Sézary cells and P140 was also found in skin-infiltrating cells of patients with SS (1715).
Histogenesis
The postulated cell of origin is a mature peripheral T cell which has skin-homing properties and exhibits a helper-cell phenotype.

Somatic genetics
Recurrent chromosomal translocations have not been detected in Sézary syndrome, but complex clonal numerical and structural chromosomal abnormalities are common and associated with a poor prognosis (1505,2343). M-FISH techniques have shown a high rate of unbalanced translocations and associated deletions often involving chromosomes 1p, 10q, 14 and 15 (1505). CGH studies have identified a consistent pattern of chromosomal gains/deletions (1p, 10q, 13q, 19, 17p losses and 4q, 17q and 18 gains) which, with the exception of 17q gains in Sézary syndrome, are identical to mycosis fungoides suggesting a similar pathogenesis (1210,1504). Allelic losses on 1p, 9p, 10q and 17p have been confirmed by LOH studies and a high rate of microsatellite instability (MSI) has also been detected (2079, 2080). These findings suggest that dysregulated genes at these chromosomal loci are involved in the pathogenesis (1554,2078). There is a high rate of genomic instability as indicated by the presence of chromosomal instability (1505). Constitutive activation of Stat 3 and chromosomal amplification of JUNB, a member of the AP-1 transcription factor complex, have been identified in Sézary syndrome (1089,1506). A recent cDNA array study in Sézary syndrome has confirmed the presence of JunB overexpression and has also revealed overexpression of other genes associated with a TH2 phenotype such as Gata-3 and RhoB (1211). These array findings appear to allow the identification of a poor prognostic group (1211).

Prognosis and predictive factors
Sézary syndrome has a poor prognosis with a median survival of 2 to 4 years depending on the exact definition used (777,1271,2044,2523). Absolute Sézary cell count and lymph node involvement are independent prognostic factors. In addition, large cell transformation and the development of skin tumours on a background of erythroderma are poor prognostic signs.

Fig. 4.20 Diagnostic pathways for the differential diagnosis of erythroderma. Algorithm for the evaluation and diagnosis of erythroderma due to cutaneous T-cell lymphoma (E-CTCL) vs. 'reactive' causes of erythroderma. TCR, T-cell receptor. *A CD4/CD8 ratio >10 or an absolute Sézary cell count of 1 109/L have been proposed as diagnostic criteria for Sézary syndrome (SS), but this algorithm requires additional immunophenotypic or genotypic data. Even so, a Sézary cell count > 1 109/L or a CD4/CD8 ratio > 10 increases the probability of neoplasia, and separates SS from E-CTCL with a lesser degree of blood involvement. **Abnormal T-cell immunophenotype = an increased population of CD4+ cells that are CD26 (>30%) or p140+. CD7 is less reliable. Aberrant T-cell immunophenotype = loss of pan T-cell markers such as CD2, CD3 or CD5, and/or double-negative T cells (CD4 and CD8). In skin, the loss of CD7 from epidermal lymphocytes is CTCL specific.

Granulomatous slack skin

Definition
Granulomatous slack skin (GSS) is clinically characterized by the development of bulky skin lesions in the major skin folds and histologically by a granulomatous infiltrate composed of small lymphocytes and scattered multinucleated giant cells containing nuclei arranged in a wreath-like fashion.

Synonyms
Progressive atrophying chronic granulomatous dermohypodermitis

Epidemiology
GSS is a rare form of primary cutaneous T-cell lymphoma. GSS usually appears in the third or fourth decade, but can also affect children (373). GSS occurs almost exclusively in Whites. The male to female ratio is 2:1 to 3:1 (490).

Clinical features
GSS begins with slightly infiltrated, poikilodermatous sharply demarcated patches and plaques. Predilection sites are the intertriginous areas, especially the axillary and inguinal folds. After years, pathognomonic bulky pendulous skin folds develop as a result of progressive destruction of elastic fibres. The lesions then resemble cutis laxa. Occasionnally ulceration occurs. Regional lymphadenopathy may be present. In contrast to granulomatous MF, GSS is in almost all cases confined to intertriginous areas, and runs a more benign course than classic MF (1387).

Histopathology
Early lesions of GSS display a bandlike infiltrate of small lymphocytes without significant nuclear atypia (1379). More advanced lesions show a dense lymphocytic infiltrate throughout the entire dermis. Nuclear atypia of lymphocytes is less pronounced than in granulomatous MF. The diagnostic hallmark is numerous multinucleated histiocytic giant cells, which are scattered throughout the background of the dense lymphocytic infiltrate. These giant cells contain 20-30 nuclei located at the periphery of the cytoplasm. Elastophagocytosis and emperipolesis (phagocytosis of lymphoid cells by giant cells) are present. Elastic stains demonstrate the loss of elastic fibres at the sites of the infiltrates in all dermal layers. On occasion, involvement of large vessels occurs. Ultrastructurally, the lymphocytes show hyperchromatic cerebriform nuclei similar to those seen in mycosis fungoides and Sézary syndrome (490). Specific infiltration of regional lymph nodes or internal organs exhibiting similar features as in the skin has been observed in rare cases.

Immunoprofile
The lymphoid tumour cells display a T helper phenotype with expression of CD3, CD4 and CD45RO. There may be loss of other T-cell markers like CD5 or CD7. In rare cases, the tumour cells express CD30.

Genetics
Clonal rearrangement of TCR genes can be found in most cases and is a useful diagnostic tool in early stages of the disease (1382). Trisomy 8 has been reported in two cases (136,2442).

Histogenesis
The tumour cells represent skin-homing T-helper cells.

Prognosis and predictive factors
The disease has a long natural history with a slowly progressive course over decades. Occasionally involvement of regional lymph nodes is found, but does not seem to affect survival. Although life expectancy is not reduced by GSS per se, other cutaneous and nodal lymphomas such as mycosis fungoides, Hodgkin lymphoma and peripheral T-cell lymphomas occur in approximately 20 – 50% of the patients, often years or even decades after the manifestation of GSS (202,490,1729,2413).
CD30-positive T-cell lymphoproliferative disorders (LPD) of the skin (CD30+LPD) represent a distinctive group of primary cutaneous T-cell lymphoma. The spectrum of CD30+ LPD includes lymphomatoid papulosis (LyP), primary cutaneous anaplastic lymphoma (C-ALCL) and borderline cases which differ in their clinical and histological presentations (191, 1174,1225,1795,2520).

A feature common to all is the expression of CD30, a cytokine receptor belonging to the tumour necrosis factor receptor superfamily. The term ‘borderline lesions’ has been applied to lesions that show clinical presentation of one entity (e.g. C-ALCL) but histological features of another one (e.g. LyP). This discrepancy may result in difficulties to assign such lesions to a distinct entity. Clinical presentation plays a crucial role in such discordant cases.

**Lymphomatoid papulosis (LyP)**

**Definition**
LyP is a chronic recurrent lymphoproliferative skin disease with self-regressing papulo-nodular skin lesions and atypical lymphoid cells in a polymorphous inflammatory background (1466).

**ICD-O code** 9718/1

**Epidemiology**
LyP is a rare disease with an estimated prevalence of 0.1 to 0.2 cases per 100,000 and a male to female ratio of 1.5:1 (2456). Mostly people in the third and fifth decades are affected, but children can also be involved.

**Localization**
Although no definite predilection site has been identified, LyP lesions more often arise on the trunk, especially the buttocks, and extremities.

**Etiology**
The cause of the disease is unknown. Endogenous retroviral elements have been identified in LyP lesions (1242). Interaction of CD30 and CD30L as well as TGF-beta and its receptor play an important role in growth regulation, including regression of tumoural lesions (1177,1648).

**Clinical features**
LyP is characterized by grouped or disseminated asymptomatic papules and/or nodules, which regress spontaneously after a few weeks sometimes leaving behind varioliform scars (1174). Often new lesions develop concurrently in the same or another body region. Larger nodules up to 2 cm can develop and persist for months (2524). Clinicopathologic variants of LyP include regional follicular and pustular forms (2076).

**Histopathology**
The histological features of LyP are variable and depend on the stage of the lesions and disease. Three histologic subtypes (types A, B and C) have been delineated (2524) which represent a spectrum with overlapping features (2148). In fully developed LyP lesions, there is a wedge-shaped diffuse dermal infiltrate which contains medium-sized to large pleomorphic or anaplastic lymphoid cells with irregular nuclei, sparse chromat in and mitotic activity. Some of the large atypical lymphoid cells resemble Reed-Sternberg cells. Ulceration may be present. In type A lesions, scat-
tered tumour cells are intermingled with numerous inflammatory cells such as neutrophils, eosinophils and histiocytes. Type C lesions show cohesive sheets of large atypical lymphoid cells with only a few intermingled reactive inflammatory cells. The rare type B is characterized by an epidermotropic infiltrate of small atypical lymphoid cells with cerebriform nuclei and histologically resembles mycosis fungoides. Various histologic types may be present in individual patients at the same time. Due to an overlap of histologic features between LyP and primary as well as secondary cutaneous ALCL, final diagnosis depends on correlation of clinical presentation and histologic findings.

**Immunohistochemistry**

A hallmark of the large atypical lymphoid cells is their positivity for CD30 (1173, 1227). The large atypical lymphoid cells in LyP are of T-cell origin with a CD3+, CD4+, CD8-. In 10% of the cases tumour cells express CD56+ (193). Usually CD2 and CD5 are expressed, whereas often CD7 and sometimes CD3 are absent. In addition, expression of activation markers such as HLA-DR and CD25 (interleukin 2-receptor) is found. Cytotoxic molecules such as TIA-1 and granzyme B are expressed in 70% of the cases (1342). CD56 is generally negative (968). CD15, a marker for Reed-Sternberg cells in Hodgkin lymphoma, is usually not expressed in LyP. In contrast to the tumour cells expressing CD30 as in LyP type A and type C, the small atypical lymphocytes present in LyP type B are usually negative for CD30.

**Genetics**

Clonal rearrangement of T cell receptor genes can be found in at least 40% of LyP lesions. Cytogenetic studies have demonstrated chromosomal deletions and rearrangements of chromosomes 1, 7, 9 and 10 (1813). The t(2;5)(p23;q35) translocation is not detected in LyP (613).

**Histogenesis**

LyP represents a proliferation of activated skin-homing T-cells with a unique cytotoxic phenotype (TIA-1+).

**Prognosis and predictive factors**

LyP exhibits a favorable prognosis with 5-year-survival rates of 100% (191,1795). So far, there are no data indicating that any kind of therapeutic intervention in LyP alters the natural history of the disease or prevents progression to other malignant lymphomas (650). Other cutaneous and nodal lymphomas such as mycosis fungoides, Hodgkin lymphoma and systemic or cutaneous CD30+ large T-cell lymphoma (LTCL) develop in 5-20% of patients with LyP (191,1174). Long-term follow-up is therefore recommended. These lymphomas are usually referred to as LyP-associated malignant lymphomas. They can develop prior to, concurrent with, or after the manifestation of LyP (1175) and result in a fatal outcome in 2% of patients (191). No risk factors have been identified which definitely indicate likely progression to associated lymphomas in LyP patients. So far, only fascin expression is found at a significantly higher rate in LyP cases associated with systemic lymphomas (1243).

### Primary cutaneous anaplastic large-cell lymphoma

**Definition**

Primary cutaneous anaplastic lymphoma (C-ALCL) is a neoplasm composed of large atypical lymphocytes of either pleomorphic, anaplastic or immunoblastic cytomorphology and expression of the CD30 antigen by the majority, i.e. more than 75% of tumour cells. Primary cutaneous and primary nodal CD30+ ALCL are distinct clinical entities that can have similar morphologic features and some overlap in immunophenotype, but differ in age of onset, genetic features, etiology and prognosis (600,2259,2493).

**ICD-O-code**

9718/3

**Synonyms**

Regressing atypical histiocytosis, EORTC: Primary cutaneous large cell T cell lymphoma CD30+

**Epidemiology**

C-ALCL is the second most common form of cutaneous T-cell lymphoma with an incidence of 0.1-0.2 patients per 100’000. This form of lymphoma affects
mainly people in their sixth decade with a male to female ratio of 2-3:1 \((191,1226)\), but it can also occur in childhood. C-ALCL is a common form of cutaneous T-cell lymphoma in HIV-infected individuals \((1248)\).

**Localization**
The extremities and head are predilection sites \((196,1228)\).

**Clinical features**
ALCL usually presents as an asymptomatic, solitary firm nodule which rapidly grows and often ulcerates \((1174)\). Approximately 20% of the patients have multifocal disease, i.e. two or more lesions at multiple anatomic sites \((191)\). Involvement of regional lymph nodes can occur. Other extra-cutaneous spread is rare. If there is no therapeutic intervention, spontaneous regression occurs in 10-40% of the tumour lesions \((191,1226)\).

**Histopathology**
There is a dense nodular infiltrate extending through all levels of the dermis into the subcutis. Epidermotropism may be found. The infiltrate consists of cohesive sheets of large, cells with irregularly shaped nuclei and one or multiple nucleoli and an abundant, clear or eosinophilic cytoplasm. Mitoses are frequent. Clusters of small reactive lymphocytes are found within and around the tumour. Eosinophils, plasma cells, and accessory dendritic cells usually are not prominent in C-ALCL. Variants of C-ALCL include neutrophil-rich or pyogenic CD30+ ALCL presenting histologically with small aggregations or scattered CD30+ medium to large pleomorphic lymphoid cells within an extensive infiltrate of neutrophils \((341,1549)\).

**Immunohistochemistry**
C-ALCL displays an activated T-cell phenotype with expression of T-cell associated antigens CD2, CD3, CD4 and CD45RO, activation markers such as CD25 (IL-2R), CD30, CD71 and HLA-DR, and frequent expression of cytotoxic molecules such as TIA-1, granzyme B and perforin \((290,1342)\). CD30 must be expressed by at least 75% of the large pleomorphic or anaplastic lymphoid cells. Variable loss of T cell antigens (CD2, CD3, CD5 and CD7) can be found \((1228)\). In contrast to systemic (nodal) ALCL, C-ALCL does not express EMA, but may express the cutaneous lymphocyte antigen (CLA, HECA-452) and homeobox gene HOXC5 \((243)\). C-ALCL is consistently negative for the anaplastic lymphoma related tyrosine kinase (ALK).

**Genetics**
Clonal rearrangement of T cell receptor genes is detected by Southern blot and PCR in most cases (over 90%) of C-ALCL \((1467)\). The translocation t(2;5) (p23;q35) resulting in expression of npm-alk protein (p80), which is a characteristic feature of systemic anaplastic large cell lymphomas, is rarely if ever found in C-ALCL \((228,613)\). Systemic ALCL may present with cutaneous disease, and the identification of ALK-expression is helpful in this distinction.

**Histogenesis**
Activated skin-homing T-cell.

**Prognosis and predictive factors**
C-ALCL has a favourable prognosis with 5 year-survival rates of 90% \((191,1795)\). Up to 40% of C-ALCL show spontaneous regression \((198)\). Regional lymph nodes may be involved, but the survival rate is similar to patients with skin lesions only \((191)\). Other extracutaneous spread occurs in 10% of the patients, especially in those with multiple grouped or multifocal tumour lesions with a fatal outcome in only a minority of the patients \((191)\). Spontaneous regression and age less than 60 years are associated with a better prognosis, while extracutaneous disease and higher age tend to have a worse outcome. Cytomorphology (anaplastic or pleomorphic and immunoblastic) seems not to be a prognostic factor \((191,1795)\).
Subcutaneous panniculitis-like T-cell lymphoma

Definition
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a T-cell lymphoma with preferential infiltration of subcutaneous tissue by atypical lymphoid cells of varying size, often with marked tumour necrosis and karyorrhexis.

ICD-O code
9708/3

Historical annotation
In the historical literature, most cases of SPTCL were probably diagnosed as histiocytic cytophagic panniculitis (562, 1527).

Epidemiology
Subcutaneous panniculitis-like T-cell lymphoma is a rare form of lymphoma, representing less than 1% of all non-Hodgkin lymphomas. It occurs in males and females equally, and has a broad age range. Cases have been reported in children under the age of two years. Most cases occur in adults (1060, 1341, 2026, 2480).

Etiology
Unknown. In most patients the disease presents sporadically.

Localization
Patients present with multiple subcutaneous nodules, usually in the absence of other sites of disease. The most common sites of localization are the extremities and trunk.

Clinical features
Clinical symptoms are primarily related to the subcutaneous nodules. The nodules range in size from 0.5 cm to several cm in diameter. Larger nodules may become necrotic, but ulceration of cutaneous lesions is rare. Systemic symptoms, most commonly fever, are variable but usually present. Some patients may present with a haemophagocytic syndrome with pancytopenias, fever, and hepatosplenomegaly (338, 863, 2480). Lymphadenopathy is usually absent.

Histopathology
The infiltrate extends diffusely through the subcutaneous tissue, usually without sparing of septae. The overlying dermis and epidermis are typically uninvolved. The neoplastic cells range in size from small cells with round nuclei and inconspicuous nucleoli to larger transformed cells with hyperchromatic nuclei. The lymphoid cells have a moderate amount of pale-staining cytoplasm. A helpful diagnostic feature is the rimming of the neoplastic cells surrounding individual fat cells (1341). Admixed reactive histiocytes are frequently present, particularly in areas of fat infiltration and destruction. The histiocytes are frequently vacuolat-ed, due to ingested lipid material. Vascular invasion may be seen in some cases, and necrosis and karyorrhexis are common. However, the infiltrates usually are confined to the subcutaneous tissue, with sparing of the dermis. This feature is helpful in the differential diagnosis from other lymphomas involving skin and subcutaneous tissue. The necrosis is primarily apoptotic in nature, possibly related to the release of cytotoxic molecules (1341, 2133). Cutaneous γδ T-cell lymphomas can have a panniculitis-like component, but commonly show both dermal and epidermal involvement in addition to subcutaneous disease (1060, 1341, 2026, 2366). Plasma cells and reactive lymphoid follicles are generally absent, in contrast to lupus profundus panniculitis, and other forms of lobular panniculitis.

In some cases of SPTCL the infiltrates in initial phases may appear deceptively benign, and the differential diagnosis with benign panniculitis may be difficult (338, 863).

Immunoprofile
SPTCL is derived from αβ cells, T-cells with a cytotoxic profile. The cells are usu-

Fig. 4.28 Subcutaneous panniculitis-like T-cell lymphoma (SPLTCL). A Erythematous plaques and nodules on the leg with ulceration. B Diffuse infiltration of subcutaneous tissue simulating lobular panniculitis. Large atypical cells rimming around fat lobules.
ally CD8-positive, with expression of cytotoxic molecules including granzyme B, perforin, and T-cell intracellular antigen (TIA-1) (1341,2026). However, in contrast to other cytotoxic TCLs related to the innate immune system (enteropathy-type T-cell lymphoma, extranodal NK/T-cell lymphoma), the cells are negative for granzyme M (metase) (694, 1122,1325,2564). The neoplastic cells are capable of producing a number of cytokines and chemokines, a feature that is related to development of systemic symptoms and the haemophagocytic syndrome (338,2340). Cutaneous γδ T-cell lymphomas (119,338,1341,2026) are distinguished from SPTCL, even if a panniculitis-like component is present.

**Histogenesis**
Mature cytotoxic T-cell of the adaptive immune system.

**Precursor lesions**
Oligoclonal T-cell populations may be found in some cases of lobular panniculitis, suggesting the potential for clonal evolution in rare cases (1484). However, progression from cytophagic panniculitis without monoclonality to SPTCL rarely if ever occurs (1527).

**Somatic genetics**
The neoplastic cells show rearrangement of T-cell receptor genes, and are negative for Epstein Barr sequences.

**Prognosis and predictive factors**
Dissemination to lymph nodes and other organs is uncommon and usually occurs late in the clinical course. The natural history is often aggressive (694,863,917, 1300,2026). A haemophagocytic syndrome is a frequent complication in αβ cases and usually precipitates a fulminating downhill clinical course. However, if therapy for the underlying lymphoma is instituted and is successful, the haemophagocytic syndrome may remit.
Primary cutaneous peripheral T-cell lymphoma, unspecified

Definition
A heterogeneous group of cutaneous T-cell lymphomas that do not fit into one of the well-defined subtypes of T-cell lymphoma/leukaemia. Three provisional entities have been separated: Cutaneous γδ T-cell lymphoma, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma and primary cutaneous small-medium CD4+ T-cell lymphoma.

ICD-O code 9709/3

Synonyms and historical annotation
The category of the peripheral T-cell lymphomas, unspecified (PTL) was introduced in the REAL classification {960} and was maintained in the WHO classification {1369}. It encompasses per definition all T-cell neoplasms that do not fit into any of the better defined subtypes of T-cell lymphoma/leukaemia. As such it constitutes a heterogeneous group of diseases. These conditions are most frequently systemic {1121}. Primary cutaneous PTL are rare and constitute less than 10% of all cutaneous T-cell lymphomas (CTCL) in large series {195}. They correspond to the CD30-negative CTCL in the EORTC classification and show an aggressive behaviour in most cases {195,2523}. Therefore, distinction between "primary" and "secondary" cutaneous involvement seems less important for this category.

Although it is still controversial how these tumours can be grouped into separate diseases, recent investigations have suggested that some disorders within this broad group of neoplasms can now be separated out as provisional entities. For the remaining diseases that do not fit into either of these provisional entities (Table 4.1), the designation PTL, unspecified, is maintained.

Cutaneous γδ T-cell lymphoma

Definition
Cutaneous γδ T-cell lymphoma (CGD-TCL) is a lymphoma composed of a clonal proliferation of mature, activated γδ T-cells expressing a cytotoxic phenotype. This group includes cases of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with a gamma/delta phenotype. In the WHO classification 2001, these were grouped together with SPTCL of αβ origin {1121}, but they show distinctive features and seem to be more closely related to other CGD-TCL {192,1060,1533,2026,2366}. A similar and possibly related condition may present primarily in mucosal sites {98}. Whether cutaneous and mucosal γδ TCLs are all part of a single disease, i.e. muco-cutaneous γδ TCL, is not yet clear {1122,2539}.

Epidemiology
CGD-TCLs are rare, with approximately 50 cases reported {1533,1665,2366}. In one series they represented <5% of cutaneous T-cell lymphomas {1879}. Most cases occur in adults. There is no reported sex predilection.

Table 4.1

<table>
<thead>
<tr>
<th>Skin lesion</th>
<th>Pattern of infiltration</th>
<th>Cytology</th>
<th>Phenotype</th>
<th>EBV</th>
<th>Behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>γδ-TCL</td>
<td>Patches, plaques, tumours, disseminated</td>
<td>E, D, S</td>
<td>Medium-large, pleomorphic</td>
<td>TCRd1+, CD3+, CD4-, CD8+, CyAg+, CD56 +/−</td>
<td>A</td>
</tr>
<tr>
<td>AEC8+</td>
<td>Eruptive nodules, hyperkeratotic plaques, disseminated</td>
<td>E</td>
<td>Medium-large pleomorphic</td>
<td>bF1+, CD3+, CD4-, CD8+, CyAg+</td>
<td>A</td>
</tr>
<tr>
<td>PTL, CD4+</td>
<td>Solitary nodules, tumours</td>
<td>D, S</td>
<td>Small-medium pleomorphic</td>
<td>bF1+, CD3+, CD4+, CD8-</td>
<td>I</td>
</tr>
</tbody>
</table>

Abbreviations: γδ-TCL= gamma delta-T-cell lymphoma; AEC8+= aggressive, epidermotopic, CD8+ cytotoxic T-cell lymphoma; E=epidermal; D=dermal; S=subcutaneous; CyAg= cytotoxic antigens (TIA-1, granzyme B, perforin); EBV= Epstein-Barr Virus; A =aggressive; I=indolent.
Etiology
The distribution of disease reflects the localization of normal γδ T cells, which are believed to play a role in host mucosal and epithelial immune responses (268). Impaired immune function associated with chronic antigen stimulation may predispose to the development of mucosal and CGD-TCLs (98,2539). Epstein-Barr virus (EBV) is generally negative in CGD-TCLs, but may be positive in primary γδ TCL in mucosal sites (98,1191,2366,2539).

Clinical features
The clinical presentation is variable. The disease may be predominantly epidermotropic and present with patches/plaques, or it may be predominantly subcutaneous with necrotic nodules or plaques, resembling panniculitis-like T-cell lymphoma (SPTCL) of γδ type (192,221,1060,1533, 1665,1879,2026,2366). The lesions are often mainly present on the extremities (2366), but other sites may be affected as well (1533,2365). Patients with CGD-TCL usually lack involvement of lymph nodes, spleen, and bone marrow, but the disease may disseminate to extranodal/mucosal sites. A haemophagocytic syndrome may occur in patients with panniculitis-like tumours (119,2365).

Histopathology
The neoplastic cells are generally medium to large in size with coarsely clumped chromatin (2366). Large blastic cells with vesicular nuclei and prominent nucleoli are infrequent. Apoptosis and necrosis are common, often with angioinvasion (1533). Three major histologic patterns of involvement are present: epidermotropic, dermal, and subcutaneous. However, usually more than one histologic pattern is present in the same patient in different biopsy specimens or within a single biopsy specimen (2366). Epidermal infiltration may occur as mild epidermotropism to marked pagetoid reticulosis-like infiltrates (221,1665,1879). Subcutaneous nodules may be panniculitis-like or more solid in appearance and may show rimming of fat cells, similar to SPTCL of alpha/beta origin (1533). Dermal and epidermal involvement often coexists with subcutaneous disease, in contrast to SPTCL of γδ origin, which is mainly or exclusively subcutaneous in distribution (192,1060,2026).

Immunoprofile
The cells are CD3+, CD2+, CD7 +/-, but usually negative for CD5 (2539). Most CGD-TCLs lack both CD4 and CD8, but some are CD8+ (2366). The cells are positive for TCR-δ, but lack βF1 of the αβ T-cell receptor. The absence of βF1 may be used to infer a γδ origin under appropriate circumstances (1151,2026,2365). The cells are positive for TIA-1 and the cytotoxic proteins granzyme B, granzyme M, and perforin. (1325,1341, 1533). CD56 is frequently expressed (1533).

Histogenesis
Functionally mature and activated cytotoxic γδ T-cells of the innate immune system.

Somatic genetics
The cells show clonal rearrangement of the TCR gamma gene. TCR beta may be rearranged or deleted, but is not expressed. Cases with predominant subcutaneous involvement express Vδ2, but this has not been studied in other CGD-TCL (1860,2026). EBV is generally negative in primary CGD-TCL (98,119).

Prognosis and predictive factors
Patients have aggressive disease resistant to multiagent chemotherapy and/or radiation (1665,2366). In a recent series of 33 patients, 22 (66%) died within 5 years of diagnosis, and in the same study TCRδ1 expression was an independent predictor of survival (2366). Among 33 patients with CGD-TCL, there was a trend for decreased survival for patients who had subcutaneous fat involvement in comparison with patients who had epidermotropic or dermal disease only. Age, sex, and lymphadenopathy did not have any discernible prognostic impact (2366).

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

Definition
A cutaneous T-cell lymphoma characterized by epidermotropic infiltrates of CD8-positive, cytotoxic T-cells of αβ origin. The behaviour is aggressive in most cases (223).

Epidemiology
This disease occurs mainly in adults and is rare with approximately 30 cases published worldwide (36,192,223,1533, 2062).

Clinical features
The clinical presentation is characterized by sudden eruptions of localized or disseminated papules, nodules and tumours, often with central ulceration and necrosis. Superficial, hyperkeratotic patches and plaques may also be present (36,223). The disease may resemble epidermotropic variants of other cutaneous T-cell lymphomas and is similar, if not identical to cases described as generalized pagetoid reticulosis of the Ketron-Goodman type (1252,1533). Classical MF, which may express CD8 in rare cases (1456,1880, 2062,2510), usu-
ally does not show overt destruction and necrosis and has a more protracted behaviour with progression over years from patches to plaques and tumours. The disease may disseminate to other visceral sites (lung, testis, central nervous system, oral mucosa), but lymph nodes are often spared (223).

**Histopathology**
The histological and cytological appearance is very variable ranging from a lichenoid pattern with marked, pagetoid epidermotropism and subepidermal edema to deeper, more nodular infiltrates. The epidermis may be acanthotic or atrophic, often with necrosis, ulceration and blister formation (36,223). Invasion and destruction of adnexal skin structures are commonly seen (1533). Angiocentricity and angioinvasion may be present (1533). Tumour cells are small-medium or medium-large with pleomorphic or blastic nuclei (223).

**Immunoprofile**
The tumour cell have a \( \beta F1^+, CD3^+, CD8^+, \) Granzyme B+, perforin+, TIA-1+, CD2-, CD4-, CD5-, CD7-/+ phenotype (36,223,2062). EBV is generally negative (192,1533).

**Histogenesis**
Skin homing, CD8-positive, cytotoxic T-cells of \( \alpha\beta \) type.

**Somatic genetics**
The neoplastic T-cells show clonal TCR gene rearrangements. Specific genetic abnormalities have not been described.

**Prognosis**
These lymphomas have an aggressive clinical course with a median survival of 32 months (36,223,1533,2062).
Primary cutaneous peripheral T-cell lymphoma, unspecified

187

phomas that originate from mature, transformed T-lymphocytes and that do not fit into any of the better defined subtypes of mature cutaneous T-cell neoplasms. Hence, other categories of T-cell lymphoma must be excluded. These include the 3 provisional entities described above. Furthermore, given the wide variety of histologic appearances of tumour stage mycosis fungoides (MF), a diagnosis of MF should always be ruled out by complete clinical examination and an accurate clinical history.

Epidemiology
These tumours account for 5 to 10% of all primary cutaneous T cell or NK cell lymphomas (195). All ages may be affected, but the disease is most common in adults.

Clinical features
Most lymphomas in this category present with rapidly growing tumours or nodules that may be multiple or (more rarely) solitary or localized (195,197,878,2523). No sites of predilection have been recorded.

Histopathology
Skin infiltrates are most often diffuse, but nodular or band-like patterns can be seen. Epidermotropism is mild or absent in most cases. The tumour cells are medium to large, usually with markedly pleomorphic nuclei. Rare cases may show a predominance of cells that are more immunoblastic in appearance (197,2523). Small reactive lymphocytes, eosinophils and plasma cells may be present (195), but the inflammatory background is usually not as pronounced as it can be in nodal malignancies.

Immunoprofile
The tumour cells express T-cell associated antigens (CD2, CD3, CD5), but usually lack CD7; most cases are CD4+, but rare tumours may be CD8+ or positive (or negative) for both CD4 and CD8 (195). Cytotoxic antigens (TIA-1+, granzyme B) are usually not expressed (195). Occasional tumour cells may be CD30-positive.

Histogenesis
Skin homing T-cells.

Precursor lesion
There are no known precursor lesions. As mentioned, cases of transformed MF may closely resemble peripheral T cell lymphoma unspecified and can only be distinguished on clinical grounds.

Somatic genetics
The TCR genes are clonally rearranged. No consistent cytogenetic abnormalities have yet been identified.

Prognosis and predictive factors
The prognosis is poor with 5-year survival rates of less than 20% (195,878). Cases with immunoblastic morphology may have an even more aggressive behaviour (197,2523). Cases with solitary/localized lesions seem to behave just as aggressively as those with multiple lesions (195).
Fig. 4.37 Primary cutaneous peripheral T-cell lymphoma, unspecified. A Grouped and B disseminated skin lesions. C The dermal neoplastic infiltrate is dense and D consists of large, pleomorphic cells with irregular nuclei and numerous mitoses.
Cutaneous adult T-cell leukaemia / lymphoma

Definition
Adult T cell leukaemia / lymphoma (ATLL) is a malignancy of mature CD4+ T cells caused by the human T-cell leukaemia virus type I (HTLV-1).

ICD-O code 9827/3

Synonyms
Adult T-cell leukaemia (ATL)

Epidemiology
ATLL is endemic in some regions of the world, especially in southwest Japan, the Caribbean islands, South America, and parts of Central Africa (1848,2392).

Etiology
ATLL develops in 1% to 5% of individuals infected with HTLV-1 after more than 2 decades of viral persistence. In most patients viral exposure occurs early in life, and incidence figures are related to the place of birth, not residence. HTLV-1 proviral DNA is monoclona

Localization
Based on organ involvement and severity, ATLL is divided into four clinical categories: acute, chronic, lymphoma, and smoldering types (2171). Cutaneous involvement is seen in up to 50% of patients. Lymph nodes, liver and spleen are frequently involved.

Clinical features
Patients with ATLL exhibit various cutaneous manifestations. The most frequent manifestation is nodules/tumours (33.9%), followed by red papules (22.6%), erythematous plaques (19.4%) and macules (6.5%) (2142). Nodules/tumours usually occur as solitary or several lesions on limited sites, whereas multiple papules tend to be distributed over large areas of the body. Subcutaneous tumours (4.8%), erythroderma (3.5%), and purpura (1.6%) are less frequent, and alopecia, folliculitis, erythema multiforme, and prurigo are rarely seen. In addition to the four clinical types, the cutaneous type of ATLL has been proposed to indicate skin-limited lesions without lymph node involvement or leukaemic involvement (1144). ATLL limited to the skin may be considered part of the smouldering type. Two patterns of skin involvement are seen; i.e., tumoural and erythematopapular. The tumoural subtype has been reported to have a worse prognosis than the erythematopapular one.

Histopathology
Individual skin lesions of ATLL exhibit varying degrees of tumour cell infiltration from the epidermis to subcutaneous tissue. Epidermotropism of the malignant T-cells is present in the majority of cases,
and even Pautrier microabscesses, indistinguishable from those of mycosis fungoides and Sézary syndrome, are often seen. The cells have medium- to large-sized pleomorphic nuclei, and occasionally show mitoses. Nuclear irregularity may be marked, with polynucleated flower cells often seen in the blood and tissues. Eosinophils may be intermingled with lymphocytes. In some cases, the tumour cells infiltrate mainly in the subcutaneous tissue (2142,2171).

**Immunohistochemistry**

In general, the malignant T cells are positive for CD3, CD4, CD25, and CD45RO but negative for CD7, CD8, CD19, and CD20 (2171). CD30 expression may be seen in larger transformed cells.

**Prognosis and prognostic factors**

The prognosis of ATLL patients with skin lesions is dependent on clinical and histological factors, and relates to the four main clinical subtypes. It has been suggested that cases of the smoldering type of ATLL have a poorer prognosis if there are deep dermal cutaneous infiltrates, as compared to cases in which skin manifestations are absent, or only present as superficial infiltration (2142).

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**Fig. 4.39** Adult T-cell leukaemia/lymphoma (ATLL). A Erythematous macule, showing infiltration of atypical lymphocytes in the upper dermis with Pautrier microabscess. B Tumour, massive infiltration of pleomorphic lymphocytes in the dermis.
Extranodal NK/T-cell lymphoma, nasal-type

Definition
Extranodal NK/T-cell lymphoma, nasal-type, is an EBV+, nearly always extranodal lymphoma of small, medium or large cells usually with an NK-cell, or more rarely cytotoxic T-cell phenotype. The skin is the second most common site of involvement after the nasal cavity/nasopharynx, and skin involvement may be a primary or secondary manifestation of the disease.

ICD-O code: 9719/3

Synonyms
REAL: angiocentric T-cell lymphoma; EORTC used to include in CTCL, large cell, CD30- and CTCL, pleomorphic, small/medium-sized

Epidemiology
Extranodal NK/T-cell lymphoma is a rare disease occurring in adults, with a male predominance. This lymphoma is more prevalent in Asia, Central America and South America.

Etiology
It is universally associated with EBV, and genetic factors play a role in susceptibility to the disease (443,1689).

Localization
The majority of patients present with skin lesions affecting more than one anatomical region, most commonly the trunk and extremities (443,1660).

Clinical features
Cutaneous involvement consists of tumour nodules and plaques. Systemic symptoms such as fever, malaise and weight loss are common. Some cases are accompanied by a haemophagocytic syndrome. The disease is closely related to aggressive NK-cell leukaemia, which also may have cutaneous manifestations, and is also EBV-associated.

Histopathology
A dense dermal infiltrate is often centred on the skin appendages and blood vessels resulting in a column-like low power appearance (1689). Prominent angiocentricity and angiodestruction are often accompanied by extensive necrosis (443,1689). Extension into the subcutis is common. Approximately 30% of cases show at least focal epidermotropism (1689). The mitotic rate is high and apoptotic bodies are numerous. NK/T-cell lymphoma has a broad cytologic spectrum ranging from small to large cells, with most cases consisting of medium sized cells. The cells often exhibit irregular nuclear folds, moderately dense chromatin, and pale cytoplasm.

Immunoprofile
The most common immunophenotype is: CD2+, CD56+, surface CD3-, cytoplasmic CD3ε+, CD43+ and cytotoxic granules + (TIA-1, granzyme B, perforin) (1325). Occasional cases are CD56-, but then require EBV positivity or presence of cytotoxic granules for diagnosis; otherwise they should be classified as peripheral T-cell lymphoma, unspecified. LMP-1 is inconsistently expressed, with EBER in situ hybridization preferred for diagnosis.

Genetics
The T-cell receptor is usually in germline configuration.

Prognosis and predictive factors
Extranodal NK/T-cell lymphoma presenting in the skin is a highly aggressive tumour with a median survival of less than 15 months (443,1660). The most
important factor predicting poor outcome is the presence of extracutaneous involvement at presentation (1660). Preliminary data indicate that co-expression of CD56 and CD30 may be associated with a better prognosis (1660,1690).

**Hydroa vacciniforme-like cutaneous T-cell lymphoma**

**Definition**
Hydroa-vacciniforme-like cutaneous T-cell lymphoma is a rare EBV-associated lymphoma of cytotoxic T-cell or NK-cell origin that affects children, characterized by a vesiculopapular skin eruption that clinically resembles hydroa vacciniforme.

**Synonym**
Angiocentric cutaneous T-cell lymphoma of childhood

**Epidemiology**
Hydroa vacciniforme-like CTCL affects children and teenagers, with almost all reported cases being from Latin America (such as Peru, Bolivia, Mexico) (166, 1479,1991) and Asia (such as Korea and Japan). Boys and girls are affected in an equal ratio (471,765).

**Etiology**
The strong association with EBV suggests a pathogenetic role of the virus and genetic predisposition, as in extranodal NK/T-cell lymphoma. The anatomic distribution of the skin lesions suggests sun exposure as a risk factor although tests for minimal erythema doses are usually within normal limits.

**Localization**
The lesions occur predominantly in sun-exposed areas, particularly the face and limbs.

**Clinical features**
Patients present with facial and hand oedema and a papulovesicular eruption that affects sun-exposed and to a lesser extent sun-protected areas. Individual lesions start with oedema and erythema and then progress to vesicles, necrosis, ulceration, crusts, and heal as varicelliform scars. Fever, wasting, hepatosplenomegaly, lymphadenopathy and hypersensitivity to insect bites are common. Some cases are accompanied by a haemophagocytic syndrome. The disease may progress to lymph node and visceral involvement.

**Histopathology**
The infiltrate consists of medium-sized atypical lymphoid cells set in an inflammatory background. The depth of the infiltrate seems related to the age of the lesion (166). A fully developed lesion shows a dense dermal infiltrate with epidermotropism and extension into the fat in a lobular fashion. Ulceration is common. The infiltrate is often angiotropic/angioinvasive and in addition may display a periadnexal and perineural growth pattern.

**Immunoprofile**
The tumour cells are cytotoxic T-cells, that have often lost expression of some pan T-cell markers. The most common phenotype is: CD2+, CD3+, CD8+, CD43+, CD45RO+, TIA-1+, Granzyme B+; CD4-, CD5-, CD7-. CD56 is variably positive, but CD57 is negative. CD30 reactivity can be seen in a subset of cells (<30%).

**Somatic genetics**
The T-cell receptor gene is clonally rearranged (166,1479), although in cases of NK-cell derivation, T-cell receptor genes are germline.

**Prognosis**
The prognosis is poor, with a 2-year survival rate of 36% (166).
Cutaneous involvement in primary extracutaneous T-cell lymphoma

Systemic peripheral T-cell lymphoma (PTL), unspecified, involves the skin in approximately 20-30% of the cases (836, 1453). Skin lesions may be present at diagnosis or can develop during disease progression. Lesions are most often tumours or nodules that may be solitary or multiple. No sites of predilection have been recorded. The histological and phenotypic features are identical to the systemic disease. The prognosis is very poor (104,690,836,1453).

Systemic anaplastic large cell lymphoma (ALCL)

Primary systemic anaplastic large cell lymphoma affects lymph nodes and extranodal sites, including in 20% of the cases the skin. The skin lesions may be present at diagnosis or can develop at relapse or during disease progression. The skin lesions are usually tumours or nodules that can be solitary or multiple. No sites of predilection have been recorded. The histological, phenotypic and genotypic features are identical in lymph nodes and the skin. The tumour cells are most often large with abundant cytoplasm and characteristic so-called hallmark cells with eccentric, horseshoe- or kidney-shaped nuclei often with an eosinophilic region near the nucleus. The principal morphological variants are the small cell variant and the histioyte rich variant (809). It is important to distinguish these lesions from primary cutaneous ALCL. The histological appearance of systemic cases is usually more monomorphic with infrequent tumour giant cells. The tumour cells in systemic ALCL express a cytotoxic phenotype and are positive for CD30 and EMA. CD3 is negative in more than 75% of cases (191, 1121). CD5 and CD7 are often negative. CD2, CD4 and CD43 are more useful and are expressed in a significant proportion of cases. ALK expression and t(2;5) or variant translocations involving ALK and fusion partners other than NPM are present in the majority of cases (706, 809). The natural history is aggressive but long term complete remissions can be obtained in most patients with ALK-positive disease (191).

Angioimmunoblastic T-cell lymphoma (AITL)

ICD-O code 9705/3

Skin lesions in angioimmunoblastic T-cell lymphoma (AITL) occur in half of the cases, usually as a generalized maculopapular eruption simulating viral exanthem or drug eruption, or as urticaria, purpura, erythematous plaques, prurigo-like lesions, erythroderma, erosions and necrotic lesions. The disease occurs mostly in middle-aged or elderly people without gender preponderance (787). Other findings are fever, weight loss, night sweats, lymphadenopathy, hepato- and splenomegaly, anaemia, an elevated sedimentation rate, leukocytosis, neutropaenia or thrombocytopaenia, as well as polyclonal hypergammaglobulinemia. AITL exhibits an aggressive course with a median survival ranging from 11 to 30 months and a fatal outcome in 50 to 70% of patients. Histologically, the skin lesions are characterized by nonspecific subtle superficial perivascular infiltrates composed of eosinophils and lymphocytes without atypia accompanied by hyperplasia of capillaries. Admixed plasma cells and histiocytes can be found (2087). Clonal T cell receptor rearrangement has been reported in some cases (1522). However, it is not clear whether the cutaneous manifestations are generally due to tumour cell involvement or a secondary phenomenon related to cytokine production.
Primary cutaneous marginal zone B-cell lymphoma (MZL) is an indolent lymphoma composed of small B cells including marginal zone (centrocyte-like) or monocytoid cells, lymphoplasmacytoid cells and plasma cells. It is considered part of the broad group of extranodal marginal zone B-cell lymphomas commonly involving mucosal sites (mucosa associated lymphoid tissue, MALT). Primary cutaneous immunocytoma, primary cutaneous plasmacytoma and cutaneous follicular lymphoid hyperplasia with monotypic plasma cells are considered variants of MZL.

ICD-O code 9699/3

Synonyms
EORTC (1997): Primary cutaneous immunocytoma / marginal zone B-cell lymphoma

Epidemiology
MZL most commonly affects adults aged over 40 years. There is no clear gender preponderance (132,2141).

Etiology
In Europe, Borrelia burgdorferi DNA has been identified in some cases of MZL suggesting that it may play an etiological role. (433). However, no association of Borrelia with CBCL has been found in the United States and Asia (2547).

Localization
MZL is predominantly localized on the upper extremities, and less often head and trunk.

Clinical features
In most cases, cutaneous MZL presents with red to violaceous plaques or nodules with an erythematous border (2141). Ulceration and visceral dissemination are uncommon. MZL with secondary spread to the skin is often multifocal (1418).

Histopathology
The infiltrate is characterized by residual reactive lymphoid follicles surrounded by pale staining cuffs of tumour cells. Reactive germinal centres with distinct mantle zones are commonly found in early lesions but may become colonized by tumour cells as the disease progresses. The interfollicular infiltrate is composed of small to medium-sized, centrocyte-like or monocytoid cells with slightly irregular nuclei, moderately dispersed chromatin, inconspicuous nucleoli and a rim of pale cytoplasm (2234,2362). Variable numbers of lymphoplasmacytoid cells and plasma cells are typically present at the periphery of the infiltrates or in the subepidermal area. Intranuclear PAS positive pseudoinclusions (Dutcher bodies), are commonly found, particularly in plasma cell rich forms of MZL. Diffuse infiltrates almost completely consisting of monocytoid cells, lymphoepithelial lesions with infiltration of sweat glands and the presence of very immature plasma cells should raise suspicion of secondary cutaneous involvement.

Immunoprofile
The neoplastic cells express CD19+, CD20+, CD22+, CD79a+, but are negative for CD5-, CD10-, bcl-6, CD23-, CD43 may be positive (132). In contrast to FL, the tumour cells are bcl-2+, but negative for bcl-6 and CD10 (603,1418). Reactive
germinal centres are bcl-6+ and bcl-2-. Anti-CD21 staining often reveals regular and irregular networks of follicular dendritic cells (FDC) in reactive follicles, but not associated with tumour cells. The lymphoplasmacytoid cells and the plasma cells show monotypic expression of immunoglobulin light chains. There are numerous admixed reactive T-cells.

**Precursor lesion**
Cutaneous lymphoid hyperplasia due to Borrelia infection may mimic MZL and has been postulated to represent a precursor lesion in some circumstances.

**Histogenesis**
Post germinal centre B-lymphocyte with plasmacytic differentiation and gene expression pattern (2273).

**Somatic genetics**
IgH genes are clonally rearranged. The most common translocation in gastric MZL, the t(11;18) involving the API2/MLT genes, has not been demonstrated in primary cutaneous MZL (1418, 2141, 2279). However, the t(14;18)(q32;q21) involving IGH and MALT1 was reported in approximately one third of cases in a small series. Fas gene mutations are present in a minority of cases, similar to MZL of other extranodal sites. Abnormalities of BCL10 are absent (906).

**Prognosis**
MZL shows a protracted clinical course with a tendency for recurrences. However, the prognosis is favourable with 5-year-survival rates between 90 and 100%. Transformation into diffuse large B cell lymphoma occurs infrequently (2141).
Cutaneous follicle centre lymphoma

Definition
Primary cutaneous follicle centre lymphoma (PCFCL) is defined as a tumour of neoplastic follicle centre cells (FCC), usually a mixture of small and large cleaved cells (centrocytes) and, to a lesser extent, large noncleaved cells (centroblasts) with prominent nucleoli. The growth pattern varies from follicular to follicular and diffuse to diffuse.

ICD-O Code 9690/3

Synonyms

Epidemiology
Primary cutaneous B cell lymphoma (CBCL) in Europe account for up to 25% of cutaneous lymphomas, manifesting predominantly in middle aged adults, with no gender predominance (2523), and having an incidence rate of 0.1-0.2 per 100,000 persons per year (1831). Among primary CBCL, marginal zone B cell lymphoma and FCL are by far the most common subtypes (744,1281,2576).

Etiology
The etiology of primary cutaneous FCL is unknown.

Localization
Most patients have local or regional disease. Trunk and head and neck regions are by far the most frequent localizations {429,744,2061,2523}. Presentation with multifocal skin lesions is observed in a small minority of patients.

Clinical features
The clinical presentation consists of firm erythematous to violaceous plaques, nodules or tumours of variable size. Larger nodules may be surrounded by small papules and slightly infiltrated, sometimes figurate plaques. The skin surface is smooth. Lesions may be present for months to many years (220, 2061,2523).

Histopathology
The infiltrates show a spectrum of growth patterns, with a morphologic continuum from follicular to follicular and diffuse to diffuse. The lesions are by definition composed of a mixture of centrocytes (which may be small and/or large) and centroblasts in varying proportion. Small centrocytes and a predominantly follicular growth pattern are more frequently found in small, early lesions. A predominance of large neoplastic cells, particularly large centrocytes or multilobated cells and less frequently centroblasts (not in confluent sheets), are generally found in more advanced lesions (large nodules or tumours) (2523). When morphologically identifiable, follicles are often ill-defined and show a monotonous population of FCC, lack starry sky histiocytes, and generally have an attenuated or absent mantle zone, different from cutaneous follicular hyperplasias (425, 429,603,864,1397). The infiltrates are found primarily in the dermis, with extension into subcutaneous tissue seen in larger nodules. The overlying epidermis is generally unaffected.

Immunoprofile
The cells express B-cell markers including CD19, CD20, and CD22, and may show (more often in cryostat sections)
monotypic staining for surface immunoglobulins (sIg). However, absence of detectable sIg staining is common in tumours showing a diffuse population of large FCC. In PCFCL, neoplastic cells consistently express Bcl-6 protein, while CD10 is variably expressed (often positive in follicular cases and more frequently negative in lesions with diffuse pattern of growth) \(\{425,429,823,1042,1832,2061\}\). Bcl-2 protein is usually not expressed but may be faintly positive, less than reactive T-cells \(\{38,209,425,603,774,1042,1622\}\). The follicles are associated with follicular dendritic cells, positive for CD21, CD23, and CD35. Residual, scattered FDC may be sometimes found in diffuse large cell infiltrates. Neoplastic cells are constantly CD5- and CD43-negative. Admixed T-cells may be abundant and sometimes predominant, particularly in small, early lesions.

**Histogenesis**
Mature germinal centre derived B-lymphocyte \(\{2273,2523\}\).

**Somatic genetics**
Clonally rearranged immunoglobulin genes are present. Bcl-2 gene rearrangement and t(14;18) chromosomal translocation are absent in most cases \(\{209,430,467,1622,1820,2523\}\). Inactivation of p15 and p16 tumour suppressor genes by promoter hypermethylation has been reported in about 10% and 30% of PCFCL, respectively \(\{468\}\). Chromosomal imbalances have been identified by comparative genomic hybridization (CGH) analysis in a minority of PCFCL, but a consistent pattern has not been emerged \(\{942,1503\}\).

**Prognosis and predictive factors**
Primary cutaneous FCL have an excellent prognosis (>95% 5-year survival). Local recurrences, most often near the initial site of cutaneous presentation, may develop but will not influence clinical outcome. Cytologic grade or growth pattern (follicular or diffuse) do not appear to have an impact on prognosis in patients with primary cutaneous disease. Locally directed forms of therapy, most commonly radiation or surgical excision (small, isolated lesions), are generally effective \(\{194,429,1283,1824,1825,1938,2060,2061,2202,2523\}\).

Secondary cutaneous follicular lymphoma (FL)

Patients more often present with multiple lesions in non-contiguous skin sites \(\{429,2060\}\). Unlike PCFCL, neoplastic cells strongly express CD10 and Bcl2, and show t(14;18) translocation in most cases. These secondary cutaneous forms are managed like a systemic lymphoma. Whether cutaneous involvement by FCL has an impact on prognosis is presently unknown.
Definition
Primary cutaneous diffuse large B-cell lymphomas (DLBCLs) are neoplastic proliferations showing a completely diffuse growth pattern consisting of large transformed B-cells without significant admixture of centrocytes. The most common variant, DLBCL, leg-type, usually occurs on the leg and less frequently at other sites. Other variants are referred to as DLBCL, other and comprise T-cell/histiocyte-rich LBCL, plasmablastic lymphoma and lesions that do not fulfill the criteria for a DLBCL, leg type.

ICD-O code
9680/3

Diffuse large B-cell lymphoma (DLBCL), leg-type

Epidemiology
Approximately 5-10% of cutaneous B-cell lymphomas are classified as DLBCL, leg type. The median age is around 70 years, and the tumours are more common in females than males (2432). DLBCL of the skin is rare in children (1005).

Clinical features
DLBCL, leg type occurs primarily in elderly females who present with rapidly developing multiple tumours, most commonly on the leg but sometimes at other localizations. Therefore analogous to the “nasal-type” designation for a distinct extranodal variant of NK/T-cell lymphomas, the term “DLBCL, leg-type” is chosen for all cutaneous diffuse large B-cell lymphomas with the designated cytological and immunophenotypic features. Clinically multiple disseminated or aggregated dome shaped red tumours with a firm consistency and a shiny surface without scaling are seen. Ulceration may occur in advanced stages.

Histopathology
The tumour cells diffusely infiltrate the dermis with a destructive growth pattern, often obliterating adnexal structures. The infiltrate may extend into subcutaneous tissue. The epidermis is often spared, with a Grenz zone. The infiltrate is composed of medium to large sized B cells, which are usually monomorphic in appearance. Cells may resemble immunoblasts, and less commonly centroblasts. There is usually a minimal inflammatory component and little stromal reaction.

Immunohistochemistry
The tumour cells are positive for CD20 and CD79a, negative for CD10 and CD138, have variable BCL-6 expression and are usually strongly positive for BCL-2 protein and MUM-1/IRF-4 (1797). These features have been shown in nodal DLBCL to correlate with an activated B-cell gene expression profile, which is usually predictive of a more aggressive clinical course (1041, 1977).

Histogenesis
Transformed peripheral B cell of probable post germinal centre origin (816).

Somatic genetics
The immunoglobulin genes are clonally rearranged. The BCL-2/JH translocation is absent (814,905,2472). Recent studies using gene expression profiling have identified increased expression of genes associated with cellular proliferation. The gene expression profile of the leg-type of tumour resembles that of activated B-cell type of nodal or systemic DLBCL (1041) Significant differences have not been identified among tumours of the leg-type arising in different sites (814,1797). The primary cutaneous large B-cell lymphoma of the leg-type can be seen in a variety of anatomic locations and is not restricted to the leg (1797).

Prognosis and Predictive factors
In multivariate analysis, BCL-2 expression, multiple skin lesions, and age remained independent prognostic factors. The 5-year disease-specific survival rates in BCL-2–positive and BCL-2–negative patients were 41% and 89%, respectively (P < .0001). 11,12 13 Thus, these studies support the identification of DLBCL leg type, as a clinically and biologically distinctive group.

Diffuse large B-cell lymphoma, other

Fig. 4.53 Diffuse large B-cell lymphoma. A Dome-shaped nodules and tumours without ulceration on the trunk and in the face. B Soft tumour surrounded by an erythematous infiltrate on the back. C Aggregation of non-ulcerated nodules and tumours confined to a limited area of the lower leg.
Definition
The term DLBCL, other, refers to diffuse lymphomas composed of large transformed B-cells that lack the typical features of DLBCL, leg-type, and do not conform to the definition of primary cutaneous follicle centre lymphoma. These tumours may be comprised of a monomorphic population of centroblast-like cells, but with a mixed inflammatory background. BCL-2 protein may be negative, whereas BCL-6 will usually be expressed. The presence of multiple lesions is a poor prognostic indicator; such cases must be distinguished from secondary involvement by DLBCL.

There are some primary cutaneous follicle centre lymphomas in which the majority of tumour cells are centroblasts. Previously these lesions have been categorized as DLBCL by most observers (864,877,879,1263). These lymphomas invariably contain a population of centrocytes as well as some reactive cells. A focal follicular growth pattern may be seen. Despite the predominance of centroblasts, clinical studies have suggested that these lymphomas have a benign clinical course, and may usually be treated in a conservative manner. Based on the clinical behaviour and the spectrum of cytological composition, these tumours are classified under the single heading of cutaneous follicle centre lymphoma.

T-cell / histiocyte-rich large B-cell lymphoma
T-cell / histiocyte-rich large B-cell lymphoma is an unusual morphological variant of “diffuse” LBCL (1886) that rarely occurs primarily in the skin (645,1423). It is characterized by a small number of large neoplastic B-cells (<10%), scattered within an abundant background of small reactive T-lymphocytes with or without histiocytes. Some T-cell/histiocyte-rich large B-cell lymphomas may represent progression from a more indolent B-cell lymphoma (645,2042).

Plasmablastic lymphoma
Plasmablastic lymphomas rarely may present as a primary cutaneous lymphoma. The tumour cells can be positive for Epstein Barr virus (EBV), and have a phenotype that reflects terminal stages of B-cell differentiation (CD20-, MUM-1+, CD138+, EMA+). Plasmablastic lymphomas are usually a heterogeneous group of disease entities (524) and can be encountered in settings of immunodeficiency, HIV-associated, or iatrogenic (617,985).

Secondary skin involvement by diffuse large B-cell lymphoma
Secondary skin involvement most commonly shows localisation of the disease on the trunk and the extremities (1263). The prognosis is worse than in primary DLBCL, which can be controlled by local treatment modalities, particularly if one is dealing with a single lesion.
Intravascular large B-cell lymphoma

H. Kutzner
E.S. Jaffe

Definition
Intravascular large B-cell lymphoma (IL) is a rare disease with multiorgan involvement, which also affects the skin. This extranodal subtype of diffuse large B-cell lymphoma (DLBCL) is characterized by the presence of large lymphoid cells within the lumina of small to medium-sized blood vessels, particularly capillaries and postcapillary venules. Skin is a common site of presentation, but most patients have systemic disease at time of diagnosis (696,2523).

ICD-O code 9680/3

Synonyms
Intravascular lymphomatosis; intravascular lymphoma; angioendotheliomatosis proliferans systematisata; malignant angioendotheliomatosis; angiotropic large cell lymphoma (Lukes-Collins), diffuse large B-cell lymphoma (REAL) intravascular large B-cell lymphoma (WHO).

Epidemiology
IL is rare and can occur at any age, but most patients are in their 6th – 9th decade of life. Male to female ratio is 0.8 (range 0.7 – 5.0) (2566).

Clinical features
The clinical manifestations are predominantly neurologic (85%) (214) and dermatologic (633) and are attributed to vascular occlusion. There is a notable absence of lymphadenopathy, splenomegaly or circulating lymphoma cells in the majority of cases (631,684, 837, 1257,2387). There is a plethora of different skin lesions including tender, indurated nodules, livedo-like reticulate erythema, linear erythematous streaks, and painful indurated telangiectasias. Lesions may imitate phlebitis, panniculitis, or vasculitis (1809).

Histopathology
The angiotropic lymphoid infiltrate often spares the dermis, requiring deep biopsies including parts of the subcutaneous fat. The large neoplastic lymphoid cells are usually confined to the lumina of capillaries and postcapillary venules (1809, 2513), albeit extravascular involvement may occur (1257). Tumour cells are large with vesicular nuclei, prominent nucleoli, and frequent mitoses. Fibrin thrombi in the upper and deep dermal plexus, with partial occlusion of the vascular lumina, and few entrapped hyperchromatic lymphocytes are typical of IL presenting with reticulate and livedoid erythema.

Immunoprofile
Tumour cells usually express B-cell associated antigens and may coexpress CD10 or CD5. (406,697,953,1193,1253, 2566). Although most IL present with overexpression of theBCL-2 protein (1257) they lack BCL-2 gene rearrangement (1193,2566). These cases have to be distinguished from other intravascular lymphomas of different lineages (112, 113,633,697,736,1355,2138,2143).

The precise mechanisms of lymphoid-endothelial interaction leading to vascular occlusion and thrombotic events are

Fig. 4.58 Intravascular large B-cell lymphoma. A Involvement of the cutis with livedoid palpable erythema. B Dilated dermal vessels filled with densely packed neoplastic lymphoid cells.
not clear. The intravascular trapping of lymphoid tumour cells might be the result of a defect in homing receptors and adhesion molecules on the neoplastic cells and the endothelial cells (737, 1852).

**Histogenesis**

The postulated cell of origin is a post follicle centre transformed peripheral B-cell.
Lymphomatoid granulomatosis

Definition
Lymphomatoid granulomatosis (LYG) is an angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites, composed of Epstein Barr virus (EBV)-positive B-cells, admixed with numerically predominant T-cells. The skin is the most common extrapulmonary site of involvement.

ICD-0 code  9766/1

Synonyms
Angiocentric immunoproliferative lesion (1432), angiocentric lymphoma.

Epidemiology
LYG is rare, usually presenting in adult life. It affects males more often than females (at least 2:1) (1223).

Etiology
Patients with underlying congenital or acquired immunodeficiency are at increased risk for LYG (921,949). Predisposing conditions include allo- geneic organ transplantation, Wiskott-Aldrich syndrome, human immunodeficiency virus infection, and X-linked lymphoproliferative syndrome. In patients without evidence of underlying immunodeficiency, reduced immune function can usually be demonstrated upon careful clinical or laboratory analysis (2534).

Localization
Skin is the most common site of involvement outside the lung (25-50%), but cutaneous involvement is rarely seen without pulmonary disease. Extremities and trunk are the most frequent localizations (185,393,1047,1124,1223,1560).

Clinical features
Patients usually present with signs and symptoms related to the respiratory tract (1124,1223,1426). Skin lesions consist of multiple erythematous dermal papules and/or subcutaneous nodules (185). Necrosis and ulceration are generally associated with larger nodules. Indurated plaques, lichen sclerosus et atrophicus-like lesions, and alopecia are less commonly seen (185,1129). Cutaneous lesions rarely precede pulmonary disease, and are seen either at diagnosis (30%) or later in the course (185). Other sites of involvement include brain (26%), kidney (32%), liver (29%) (1124). Lymph nodes and spleen are spared.

Histopathology
LYG is characterized by an angiocentric and angiodestructive lymphohistiocytic infiltrate. Most cutaneous lesions show infiltration of subcutaneous fat, with or without dermal involvement. Lymphocytic vasculitis is frequent, and fibrinoid necrosis may be present (2339). Well-formed granulomas are usually absent, but a granulomatous reaction may be seen secondary to fat necrosis.

Immunohistochemistry
While EBV-positive B-cells are readily found in the lung, they are generally rare in skin, with the predominant cell being a CD3+, CD4+ lymphocyte (185).

Histogenesis
Mature B lymphocyte, transformed by EBV.

Somatic genetics
The ability to detect clonal immunoglob-
ulin heavy chain gene rearrangement is related to grade, with clonal B-cell populations usually found only in grade 2-3 lesions. Southern blot, polymerase chain reaction (PCR), and in situ hybridization techniques can be used to detect EBV sequences (921,1224,1560).

**Prognosis and predictive factors**

The natural history of LYG is variable (714,1223). In some patients it may follow a waxing and waning clinical course, with spontaneous remissions without therapy. However, in most patients the disease is more aggressive, with a median survival of less than two years. Histological grade and clinical aggressiveness relate to the proportion of EBV+ B-cells, but even grade 3 lesions may show spontaneous regression (2534). The most common cause of death is progressive pulmonary involvement. Skin lesions may appear, without evidence of relapse at other sites (185,2534).
**Mantle cell lymphoma**

**Definition**
Mantle cell lymphoma is a B-cell lymphoma that almost always overexpresses cyclin D1 and is composed either of small lymphocytes bearing some resemblance to centrocytes or, in the blastoid variant, by cells resembling lymphoblasts or large B-cells. Neither classic centroblasts nor paraimmunoblasts are present.

**ICD-O code** 9673/3

**Epidemiology**
MCL occurs in middle aged to older individuals with a male predominance and accounts for up to 10% of all non-Hodgkin lymphomas (2301).

**Clinical features**
Most patients present with adenopathy and stage III/IV disease. Hepatosplenomegaly and bone marrow involvement are common and peripheral blood involvement is seen in about 25% of patients. Gastrointestinal disease is also common but often subtle (2254).

**Cutaneous MCL**
Skin involvement is rare (2-6% of cases) (2030) but when it occurs, is usually, but not always, seen at initial presentation and associated with extracutaneous disease (654,2132). Rare cases that appear to be primary are described. Lesions are most common on the thorax and extremities and usually occur as multiple erythematous macules, papules, plaques or nodules (654,2132).

**Histopathology**
MCL are usually composed of relatively small lymphocytes with slightly irregular to very clefted nuclei and somewhat dispersed chromatin. In the blastoid variant, which may be relatively more common in cutaneous lesions, the cells either have very dispersed chromatin with inconspicuous nucleoli resembling lymphoblasts, or are larger and more pleomorphic, sometimes with very prominent nucleoli, resembling cells of a diffuse large B-cell lymphoma.

MCL infiltrates in the skin occur in the dermis sometimes with extension to the subcutaneous tissue. A grenz-zone should be present. The infiltrate may be relatively scanty and perivascular/periappendageal, form nodules or be very dense and diffuse. A mantle zone growth pattern with MCL growing around reactive germinal centres may occur (219,654). Admixed inflammatory cells may be present (654).

**Immunohistochemistry**
MCL are distinguished in most cases from other non-Hodgkin lymphomas by their frequent but not invariable CD5+, CD10-, CD23-, cyclin D1+, BCL-6-, CD20+ light chain class restricted phenotype (376,2301,2303). Cyclin D1 staining can be problematic and CD5 not always positive. With one interesting exception, the cases are negative for the cutaneous lymphocyte-associated antigen (2132).

**Histogenesis**
Mature B-cell, probably of the inner mantle zone, usually but not always with unmutated immunoglobulin heavy chain genes.

**Somatic genetics**
Immunoglobulin genes show clonal rearrangement in all cases and in many, but not all, cases they lack somatic hypermutation (1756,2451). The vast majority of MCL have a t(11;14)(q13;q32) translocation involving the CCND1 (cyclin D1) and immunoglobulin heavy chain genes with subsequent CCND1/cyclin D1 overexpression (376, 2303). The most sensitive technique to document the translocation in diagnostic specimens is cytogenetic fluorescence in situ hybridization (FISH) analysis.
Gene profiling has suggested the presence of a small subset of cases that lack cyclin D1 abnormalities (1978). Other primary and mostly secondary abnormalities are also described (376,1045,2303).

**Prognosis and predictive factors**

MCL has a median survival of 3-5 years with those having “non-nodal” disease doing better (376,1756,2301,2303). Adverse prognostic indicators include a high proliferative fraction, probably blastic morphology, secondary genotypic abnormalities and blood involvement (at least in patients with nodal disease). Whether skin involvement in particular is an independent prognostic indicator is uncertain.

**Burkitt lymphoma**

**Definition**

Burkitt lymphoma is a mature B-cell neoplasm composed of relatively uniform medium sized transformed B-cells with a C-MYC translocation (630).

**ICD-O code**

9687/3

**Epidemiology**

BL occurs in children in equatorial Africa (endemic), primarily in children and young adults elsewhere (sporadic) and in immunodeficient patients. There is a male predominance.

**Etiology**

Endemic BL and a minority of sporadic BL are Epstein-Barr virus positive.

**Clinical features**

BL usually presents as an extranodal mass often in the abdomen or, in endemic cases, in jaw or other facial bones. Other patients have a leukaemic presentation. Cutaneous involvement in BL appears to be extremely rare and at least usually is associated with disease at other sites (123,141,349,700). It has rarely been described as occurring with ulceration from direct invasion from underlying bony lesions (349), as distinct cutaneous lesions at relapse (123) and in 12% of autopsied cases of American BL (2 cases) (141).

**Histopathology**

Histologic sections show a diffuse proliferation of medium sized transformed lymphocytes with relatively round nuclei with several nucleoli and a narrow rim of very amphophilic/basophilic cytoplasm. There are many apoptotic bodies and tingible body macrophages creating a starry sky appearance. Skin involvement demonstrates a diffuse but sometimes patchy dermal and subcutaneous infiltrate with a Grenz zone (123,700).

**Immunohistochemistry**

Immunophenotypic studies demonstrate CD5-, CD10+, BCL-2-, CD20+ mature B-cells with surface immunoglobulin expression.

**Histogenesis**

Germinal centre/post germinal centre B-cell

**Somatic genetics**

All cases have clonal immunoglobulin gene rearrangements and a C-MYC translocation, most often with a t(8;14)(q24;q32) (1483). Many, if not all, cases also have C-MYC mutations (230, 1483).

**Prognosis and predictive factors**

BL is an aggressive but curable neoplasm with a 5 year overall survival of 44% (3).

**Chronic lymphocytic leukaemia / small lymphocytic lymphoma**

**Definition**

Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell neoplasm composed of small, usually CD5+, CD23+, cyclin D1- B-cells with relatively round nuclei having clumped chromatin (1662). Especially in lymph nodes, there is often an associated minor population of prolymphocytes and paraimmunoblasts that form proliferation centres.

**ICD-O code**

Chronic lymphocytic leukaemia 9823/3

Small lymphocytic lymphoma 9670/3

**Epidemiology**

CLL is the most common type of leukaemia in the West and SLL are reported to account for 6.7% of non-Hodgkin lymphomas (3,1064).
Clinical features
CLL/SLL is seen most commonly in middle-aged and older adults with a male predominance. It usually presents with blood and marrow involvement, frequent adenopathy and sometimes hepatosplenomegaly. Skin involvement is reported in 2% of patients without a marked predilection for any region of the body and occurs in patients who also have blood involvement (273,1167). The face and scalp are frequent sites of involvement. It may be present either at the time of diagnosis or, much more frequently, develops subsequently (431). Lesions may be single or multiple erythematous macules, papules, violaceous plaques, nodules or tumours either occurring in a limited or less frequently more generalized area (431,1167). Atypical presentations include chronic paronychia, papulovesicular eruption and finger clubbing. Skin involvement may occur at sites of previous viral (eg, herpes zoster, herpes simplex) or Borrelia burgdorferi infection (427) and at sites of epithelial neoplasms (2215). Spontaneous regression of CLL infiltrates at least at sites of prior herpetic infection may occur (2449). In contrast to the absence of virus in at least most of the lesions in viral scars, B. burgdorferi DNA is found in at least some cutaneous CLL lesions (427).

Histopathology
Histologic sections demonstrate a diffuse proliferation of small relatively round lymphocytes with condensed chromat in with lymph node biopsies typically demonstrating paler (pseudofollicular) proliferation centres where the cells have more abundant pale cytoplasm, more dispersed chromat in and sometimes prominent central nucleoli. The latter cells represent paraimmunoblasts and some of the former cells prolymphocytes. Cutaneous lesions show a patchy perivascular, nodular, more diffuse or rarely band-like dermal infiltrate of small, usually but not always round, lymphocytes with occasional single lymphocytes in the epidermis and frequent extension into the subcutaneous tissue (431). Patients with more than one biopsy can demonstrate more than one growth pattern. There may be overlying epidermal changes infrequently including ulceration. Proliferation centres are seen only in a minority of cases although there may be scattered larger cells in other cases (431). A minority of cases have admixed eosinophils, neutrophils, and/or histiocytes. A granulomatous reaction may be present especially in some of the lesions arising in scars following prior viral infection (432). Cutaneous CLL associated with granuloma annulare-like changes has also been reported (797).

Immunoprofile
Immunophenotypic studies demonstrate a characteristic CD5+, CD43+, CD10-, CD23+, FMC7-, cyclin D1-, weakly CD20+ monoclonal B-cell population with weak surface immunoglobulin expression (1662). In the cutaneous lesions, the admixed T-cells present are mostly of CD4+ type (431).

Histogenesis
Mature B-cell most likely of memory type (including cases with either mutated or unmutated immunoglobulin heavy chain genes) (586,1288,1976).

Somatic genetics
All cases have clonal immunoglobulin gene rearrangement although oligoclonal bands suggesting admixed reactive B-cells may also be present in the cutaneous lesions (431). In some cases the immunoglobulin genes show somatic hypermutation and in others they do not (586,943,1288,1976). There are no chromosomal abnormalities specific for CLL/SLL; however, the most commonly described abnormalities include 13q and 11q deletions, trisomy 12 and 17q deletion (643).

Genetic susceptibility
There is an inherited susceptibility to CLL; however, the critical genes remain to be determined (1064).

Prognosis and predictive factors
CLL/SLL is one of the indolent lymphoid neoplasms. Clinically advanced stage, 17q deletions, unmutated immunoglobulin genes, CD38 and ZAP-70 expression include some of the more important adverse prognostic indicators (553,643,943,1662,1760,2518). Most do not believe that skin involvement portends an adverse outcome; however, it has been reported that cases with >5% medium and large-sized B-cells, admixed reactive cells and epidermal changes did worse than those without these features and there are reports in the literature suggesting a poor outcome following any cutaneous involvement (427,432,1167). Transformation to a large cell lymphoma (Richter syndrome), Hodgkin lymphoma or prolymphocytic leukaemia is also associated with an aggressive course (826). Richter syndrome can present as cutaneous lesions (427,2578).
Hodgkin lymphoma

Definition
Hodgkin lymphoma (HL) is a neoplasm characterized by large tumour cells of B-cell lineage in a characteristic inflammatory background. It encompasses two entities distinguishable by their morphology and phenotype, namely nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL). Cutaneous involvement by NLPHL has not been reported, and is rare in cHL. For details see the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (1121).

ICD-O code
Nodular lymphocyte predominant Hodgkin lymphoma 9659/3
Classical Hodgkin lymphoma 9650/3

Synonym
Hodgkin disease

Epidemiology
Cutaneous involvement by cHL is rare and is seen in <5% of cases, and <1% of cases at presentation (1076,1457, 2326,2505). The incidence appears slightly increased in patients infected with the human immunodeficiency virus (HIV) (2094,2157). cHL has also been reported to occur with increased frequency in patients with mycosis fungoides and cutaneous CD30+ T-cell lymphoproliferative disease (CD30+ LPD), but is usually nodal in localization without cutaneous spread (1123,1176,1324, 2190).

Etiology
The etiology of cHL is not established. However, an association with the Epstein Barr virus has been suggested, especially in cutaneous cases (1340).

Localization and Clinical features
Three mechanisms of cutaneous involvement have been imploed: 1) retrograde lymphatic spread from regional lymph nodes; 2) direct extension, usually from a mass lesion; and 3) haematogenous dissemination (2326,2505). The distribution of cHL lesions relates to the manner of spread. Direct extension is most common in patients with massive mediastinal disease, with involvement of the skin of the chest wall. The lesions are manifested as erythematous papules or nodules. Rare cases of HL presenting as primary disease in the skin have been reported 12 (2195).

Histopathology, immunoprofile and genotype
The histological features resemble those of cHL in other sites. Classical Reed-Sternberg (RS) cells and variants are seen in an inflammatory background. The immunophenotype also is characteristic of cHL, with the neoplastic cells expressing CD30 and CD15 (426,1340). However, while most cases of cHL are of B-cell lineage (1340), cases of cHL with cutaneous involvement may express a T-cell phenotype (595,1176,2527). Such cases are usually associated with concomitant CD30+ LPD. Common clonal T-cell gene rearrangement has been identified in the atypical cells of CD30+ LPD and cHL involving lymph nodes. Because RS-like cells may be seen in CD30+ LPD, the differential diagnosis between these disorders is often difficult.

Prognostic factors
In patients with cutaneous involvement secondary to haematogenous spread, the prognosis is poor. However, other patterns of cutaneous involvement are not necessarily associated with a poor prognosis (415,1023,1457,1651,1987, 2326,2505).

Fig. 4.65 Hodgkin lymphoma. A Secondary involvement of the skin often occurs by direct extension, as in this large cutaneous nodule with ulceration. B cHL, skin. Classical Reed Sternberg cells are present in a background of reactive lymphocytes.
Blastic NK-cell lymphoma

Definition
Blastic NK-cell lymphoma is a clinically aggressive lymphoma, with a high incidence of cutaneous involvement and risk of leukaemic dissemination. The blastic appearance and CD56 expression initially suggested an NK-precursor origin (632). More recent studies suggest derivation from a dendritic cell precursor, as reflected in the designation CD4+, CD56+ haematodermic neoplasm.

ICD-O code 9727/3

Synonyms
CD4+, CD56+ agranular haematodermic neoplasm, blastoid NK-cell lymphoma, monomorphic NK-cell lymphoma

Epidemiology
Blastic NK-cell lymphoma is a rare lymphoma. Currently, there are no reports showing any racial or ethnic predilection. Most patients are middle-aged or elderly (632,1817). However, every age can be affected.

Localization
Blastic NK-cell lymphoma has a predilection for skin. At presentation there may be a single tumour, nodule or plaque (632,1817). Lymph node, soft tissue, peripheral blood or bone marrow can be simultaneously involved. Central nervous system involvement can develop during the course of the disease.

Clinical features
Blastic NK-cell lymphoma frequently involves the skin at presentation with a single tumour, or tumours and plaques. Additionally, lymph nodes, soft tissue, peripheral blood or bone marrow can be simultaneously involved. Most cases of blastic NK-cell lymphoma presenting in the skin progress quickly to develop lymph node, bone marrow, and central nervous system involvement (450,739). The clinical course is aggressive. There may be initial responses to multiagent chemotherapy, but a high risk of relapse. Regimens for both aggressive lymphomas and acute myeloid or lymphoid leukaemias have been utilized.

Histopathology
The dermis contains a dense, monotonous infiltrate of medium-sized cells with finely clumped chromatin, and absent or indistinct nucleoli resembling lymphoblasts or myeloblasts (632,1121,1817). The cells have sparse cytoplasm. Mitotic figures are frequent. The overlying epidermis is spared, with a distinct grenz zone. Inflammatory cells are absent. There is generally no necrosis or angioinvasion.

Immunoprofile
The tumour cells usually express CD4, CD56, and CD43. Expression of CD7, CD2 is variable, whereas surface and cytoplasmic CD3 are negative (632,1817,2391). Cytotoxic molecules are generally absent. In some cases TdT and/or CD34 can be positive (313,1681,2159). CD68 can be weakly positive, showing focal staining in the Golgi region. Since lymphoblastic and myeloblastic neoplasms can also be positive for CD56, stains for myeloperoxidase, and CD3 should always be performed in order to exclude these entities (2118,2299). The cells express CD123 and TCL1, both of which support a relationship to dendritic cells (450,1012). Blastic malignancies of precursor NK-
cell origin also exist, and may be difficult to distinguish in the absence of specialized techniques (1012,1681,2302). There has been one report showing expression of KIR receptors (1293).

**Histogenesis**
Based on the expression of CD56, an NK-cell derivation was initially proposed. However, the tumour was considered to be of uncertain lineage in the WHO classification. Recently studies have suggested a derivation from plasmacytoid dendritic cells based on gene expression studies and cytokine production. The cells express high levels of interleukin-3 receptor alpha chain (IL-3R-alpha).

**Genetics**
T-cell receptor genes are in germline configuration. Tumour cells are negative for EBV.

**Prognosis and predictive factors**
Blastic NK-cell lymphoma is an aggressive disease with a poor prognosis (311,739). While close to 80% of patients obtained an initial complete remission, the majority of patients relapsed within two years. Patients with single isolated skin lesions appear to have a better prognosis (525).
Precursor T-lymphoblastic leukaemia/lymphoma and precursor B-lymphoblastic leukaemia / lymphoma

Definition
Precursor lymphoblastic leukaemia/lymphoma is a malignancy derived from precursor cells of either T-cell or B-cell lineage. There is overlap in the clinical presentation, and patients may present with disease primarily in the bone marrow and peripheral blood (leukaemia) or in solid tissues (lymphoma). Because of similarities in stage of differentiation, and manner of presentation, precursor T-cell and B-cell malignancies will be discussed together.

ICD-O code
Precursor T-lymphoblastic leukaemia 9837/3
Precursor T-lymphoblastic lymphoma 9729/3
Precursor B-lymphoblastic leukaemia 9836/3
Precursor B-lymphoblastic lymphoma 9728/3

Synonyms
Acute lymphoblastic leukaemia
Lymphoblastic lymphoma

Epidemiology
Lymphoblastic leukaemia/lymphoma is rare. Approximately 3.5% to 7% of all malignant lymphomas of the skin are of the lymphoblastic type (339,2041). Most cases are diagnosed in children and young adults. However, every age can be affected. Precursor B-cell malignancies are more common in skin than those of precursor T-cell origin (470,1431,1489,2043).

Clinical features
Lymphoblastic leukaemia/lymphoma may initially present in cutaneous or other extranodal sites as a single nodule or tumour (1429,2041). Frequent sites are the head and neck region, especially for patients with precursor B-cell disease (2043). However, there is a high likelihood of occult disease in the bone marrow, and patients should be regarded as having systemic disease for therapeutic purposes.

Morphology
The dermis contains a monotonous infiltrate composed of small to medium sized cells with fine chromatin and scant cytoplasm, characteristic of lymphoblasts. Nuclear irregularities are variable, and do not correlate with lineage. The epidermis is uninvolved, with a distinct Grenz zone. The cells are interspersed among dermal collagen fibres, without a stromal or inflammatory response.

Immunoprofile
T-cell lymphoblastic leukaemia/lymphoma. The tumour cells are positive for terminal transferase (TdT), CD43, CD99 (1489,1949,2043). They variably express CD1a, CD2, CD3, CD4, CD5, and CD8. CD10 may be positive in some cases.

B-cell lymphoblastic leukaemia/lymphoma. The tumour cells are positive for TdT, CD43, and CD99 (1489,2043). The cells are usually positive for CD19 and CD79a (326). CD10 is expressed in most cases. CD20, CD22, and CD24 are variably expressed. LCA may be negative. The cells may contain cytoplasmic µ heavy chain, usually in the absence of light chains.

Histogenesis
Precursor T- or B- lymphoblast.

Somatic genetics
Rearrangement of immunoglobulin heavy chain genes, and T-cell receptor genes usually correlates with B-cell or T-cell lineage, respectively (544,1311). However, lineage infidelity is common in precursor lymphoid malignancies. Light chain gene rearrangement is a relatively late event in B-cell differentiation.

The classification of lymphoblastic malignancies is closely related to a complex series of genetic abnormalities that correlate with pathogenesis and clinical outcome (1121).

Prognosis and predictive factors
Precursor lymphoblastic leukaemia/lymphoma is an aggressive disease. However, cutaneous involvement is not a poor prognostic factor, and response to systemic multiagent chemotherapy may be excellent (2043).
Definition
Myeloid leukaemia is a heterogenous malignant disorder of myeloid precursor cells characterized by an increase in blast forms in the peripheral blood and bone marrow. Specific skin involvement results from direct infiltration of the skin by neoplastic cells.

Synonyms
Extramedullary myeloid sarcoma, granulocytic sarcoma, chloroma.

Epidemiology
Acute myeloid leukaemia (AML) accounts for 10-15% of childhood leukaemia but the incidence increases steadily with age. More than 50% of patients are older than 60 years (1838). Chronic myelogenous leukaemia (CML) is generally a disease of older adults, with a median age between 50 and 60 years at presentation (1183). Skin involvement is reported to occur in 2% to 30% of patients with AML (35,125,649). Specific skin lesions are equally common among males and females. It is found more frequently in patients with acute myelomonocytic (AMML) and monoblastic/monocytic leukaemias (AMOL). Specific cutaneous lesions are less common in chronic myelomonocytic leukaemia (CMML) and CML.

Clinical features
Specific skin lesions present as solitary or multiple violaceous to red-brown papules, nodules and plaques. The most common sites of involvement are the scalp, face, trunk, and extremities (2288). Haemorrhagic lesions are common. Leukaemic gingival hyperplasia is a striking feature of AMML and AMOL (649). In the majority of cases, specific skin lesions develop in the setting of established leukaemia. In rare instances, leukaemic skin infiltrates may precede peripheral blood and bone marrow involvement (445,589,2368).

Histopathology
There is a moderate or dense, diffuse or nodular infiltrate in the dermis that extends into the subcutaneous fat (329,1172). The epidermis usually is spared. The infiltrates typically show perivascular and periadnexal accentuation. A characteristic feature is the presence of rows of atypical cells between collagen bundles (2137). The infiltrate is composed of medium-sized or large neoplastic cells with round, oval or folded basophilic nuclei. Mitotic figures are usually present. In CML, the infiltrate is more pleomorphic and dominated by mature and immature cells of the granulocytic series. Cutaneous infiltrates of plasmacytoid monocytes may occur in CMML (297).

Immunoprofile
The majority of the tumour cells shows reactivity for lysozyme, myeloperoxidase, CD45, CD43, and CD74. Staining for chloroacetate esterase and CD68 is variable (1172,1899). Staining for CD34 is variable, and often negative in monocytic leukaemias. The neoplastic cells are negative for CD3, CD20, CD30 and S-100 protein. The presence of CD56 expression in specific skin infiltrates of AML has been reported (1163,1258).

Histogenesis
Haematopoietic stem cells.

Somatic genetics
Genetic studies of specific cutaneous lesions in AML are scant and limited to isolated cases. An increased incidence of trisomy 8 in AML with skin infiltration has been reported (35). Rarely, cases of congenital AML may be present with skin lesions.

Genetic susceptibility
Patients with Down syndrome, Fanconi anaemia, ataxia telangiectasia, Bloom syndrome, and Kostmann syndrome are predisposed to AML.

Prognosis and predictive factors
The prognosis of patients with specific skin lesions of AML is generally poor (125,805). In one series, all patients died within 24 months after onset of skin lesions (1172).
Lymphoid infiltrates of the skin mimicking lymphoma (cutaneous pseudolymphoma)

Definition
The term pseudolymphoma (PSL) is defined as a reactive polyclonal benign lymphoproliferative process predominantly composed of either B-cells or T-cells, localized or disseminated. It heals spontaneously after cessation of the causative factor (e.g. drugs) or after non-aggressive treatment.

Synonyms and historical annotation
In 1923, Biberstein coined the term lymphocytoma cutis. Since then, a variety of designations have been proposed: lymphadenosis benigna cutis (124), pseudolymphoma of Spiegler (2237) and Fendt. (721), cutaneous lymphoid hyperplasia and lymphocytoma cutis (401). In retrospect, most of these terms were describing cutaneous B-cell pseudolymphomas (B-PSL). The concept of cutaneous T-cell pseudolymphomas (T-PSL) was not widely accepted until the early 1980’s.

Epidemiology
Cutaneous pseudolymphomas affect all age groups with a predilection of Borrelia-induced B-pseudolymphomas in children and young adults, whereas drug induced T-pseudolymphomas more frequently are seen in adults. Even though Borrelia-induced pseudolymphomas may be precursors for B-cell lymphomas of the skin, in general cutaneous pseudolymphomas are selfregressing and do not affect survival.

Etiology
Pseudolymphomatous proliferations in the skin may be induced by microbial, physical or chemical agents including Borrelia burgdoferi infection, tattoos and drugs.

Localization
In most cases, skin lesions are confined to the site of external irritation, i.e. tick bite. Due to the preferential “docking” of ticks to body areas where the skin is relatively soft, e.g., scrotum of young boys, the mamilla, ear lobes, large skin folds are preferentially involved.

Clinical features
Several variants of cutaneous PSL exist, presenting with different clinical symptoms.
Pseudolymphoma (PSL) with predominant T-cell infiltrates (T-PSL)
Lymphocytic infiltration (idiopathic or drug induced)
Palpable migratory arciform erythema
Lymphomatoid contact dermatitis
Actinic reticuloid
Persistent nodular arthropod-bite reactions
Inflammatory molluscum contagiosum

The original description of lymphocytic infiltration (idiopathic or drug induced cutaneous T-cell pseudolymphoma) given by Jessner and Kanof in 1953 (1141) is still valid today. The lesions are flat, discoid, more or less elevated, pinkish to reddish brown, starting as small papules, expanding peripherally, sometimes clearing in the centre, sometimes showing a circinate arrangement. The surface is smooth, occasionally uneven. There is no follicular hyperkeratosis as seen in discoid lupus erythematosus, which may be simulated. There may be only one, a few, or numerous lesions.

Histopathology
Characteristic is a sleeve-like, predominantly lymphocytic infiltrate around the vessels of the upper and mid dermis. In addition, some macrophages and eosinophils may be found. Phenotyping has shown the infiltrate to consist of both B and T cells (423) even though T cells seem to predominate in most cases (2521).

Palpable migratory arciform erythema clinically shows a circinate or annular slightly elevated erythematous lesion.

Table 4.02 Differentiation between B-pseudolymphoma (B-PSL) and cutaneous B-cell lymphoma (CBCL)
Taken from Burg et al. (340).

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>CBCL</th>
<th>PSL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of lesions</td>
<td>solitary or multiple</td>
<td>usually solitary</td>
</tr>
<tr>
<td>Extracutaneous involvement</td>
<td>possible</td>
<td>absent</td>
</tr>
<tr>
<td>Recurrences</td>
<td>likely</td>
<td>usually no recurrences</td>
</tr>
<tr>
<td>Survival time</td>
<td>affected</td>
<td>not affected</td>
</tr>
<tr>
<td>Histological features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pattern of infiltrate</td>
<td>diffuse or nodular, “bottom-heavy”</td>
<td>nodular (&gt;90%) “top-heavy”</td>
</tr>
<tr>
<td>Structure of infiltrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Border of the infiltrate</td>
<td>convexe, sharply demarcated “infiltrating” between collagen bundles</td>
<td>concave, poorly demarcated</td>
</tr>
<tr>
<td>Additional cells</td>
<td>usually absent</td>
<td>eosinophils, plasma cells</td>
</tr>
<tr>
<td>Transformation</td>
<td>may occur</td>
<td>never occurs</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin light chains</td>
<td>monotypic (kappa or lambda)</td>
<td>polytypic expression</td>
</tr>
<tr>
<td>B-cell marker expressing cells</td>
<td>&gt;50% cells</td>
<td>≤50% cells</td>
</tr>
<tr>
<td>T-cell marker expressing cells</td>
<td>usually few</td>
<td>&gt;50% cells</td>
</tr>
<tr>
<td>CD21-positive dendritic cells</td>
<td>mostly absent irregular pattern</td>
<td>mostly present regular pattern</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ig heavy chain gene rearrangement</td>
<td>present in most cases</td>
<td>absent in most cases</td>
</tr>
</tbody>
</table>
Histologically there is a scant sleeve-like perivascular lymphocytic infiltrate in the mid or deep dermis.

Lymphomatoid contact dermatitis has been reported as a reaction to various allergens (i.e. nickel, Peru balsam) or drugs (diphenylhydantoin) inducing mycosis fungoides-like features (1975). Genotyping has shown clonal rearrangement in some cases. Such cases may be closely related to “clonal dermatitis” some of which develop into overt CTCL (2545,2546). Histologically, eczematous features with epidermotropism of lymphocytes and accumulations of CD1a-positive Langerhans cells may be found. Actinic reticuloid is a chronic photodermatitis of light exposed areas associated bearing a clinical and histological resemblance to malignant lymphoma, especially to Sézary syndrome. Histologically there is a dense infiltrate of lymphocytes mixed with many polyclonal plasma cells, eosinophils and macrophages.

There is a considerable overlap between T- and B-PSL in persistent nodular arthropod-bite reaction, nodular scabies and inflammatory molluscum contagiosum which show a dense polymorphous infiltrate consisting of a mixture of T-cells, B-cells, macrophages and predominantly eosinophilic granulocytes.

Lymphomatoid papulosis even though showing biologic features of pseudolymphoma is considered to belong to the group of lymphomas since despite spontaneous regression of single lesions, the disease is not curable and may show transitions to other lymphomas.

**PSL with predominant B-cell infiltrates**

Lymphadenosis benigna cutis (LABC) (124) - the prototype of this group of B-PSL- is synonymous with lymphocytoma cutis. In Europe it is most commonly caused by infection with Borrelia burgdorferi after a tick bite (Ixodes ricinus). However other microbiological (medicinal leeches, Hirudo medicinalis) (2211), physical or chemical agents as well may induce lymphocytoma-like reactions.

Two thirds of all lesions are situated on the head, tendency to occur on the ear lobes. Other predilections are the nose as well as the nipples, the inguinal area and scrotum. Usually the lesion is a solitary papule or nodule, but several disseminated lesions may occur as well (1068).

Microscopic examination shows a nodular dermal infiltrate with reactive follicles. In addition, there is a rather diffuse infiltrate containing T cells, histiocytes, eosinophils and polyclonal plasma cells. The presence of macrophages containing ingested nuclear material (tingible body macrophages) within the follicles producing a “starry sky” pattern is a common feature in B-PSL and a hallmark of all reactive germinal centres. The infiltrate is predominantly located in the upper and mid dermis, but may extend into the deep dermis. Small groups of lymphoid cells between collagen bundles may be observed at the periphery of the lesions. This is a helpful histological criterion in the differentiation from cutaneous B-cell lymphoma, in which the nodular infiltrate shows convex rather than concave sharply demarcated borders.

Phenotypically (428) a polyclonal B-lymphocytic infiltrate without light chain restriction of the infiltrate is found in most cases. The cells express the phenotype of mature B-cells (CD 20, CD 79a). In B-PSL, regular and sharply demarcated networks of CD21+ follicular dendritic cells are present, whereas in CBCL these networks are irregularly shaped (342).

**Acral pseudolymphomatous angiookeratoma of children (APACHE)** is a rare benign pseudolymphomatous disorder occurring mainly in children (1888). The typical clinical presentation is multiple (up to 40), asymptomatic, small papules located unilaterally on the fingers, toes and hands. Their colour is usually red-violet, accounting for their angiomatous appearance (1887).

Histologically the dermis contains a moderately to very dense, non-epidermotropic infiltrate composed of small well-differentiated lymphocytes admixed with a few plasma cells, histiocytes, and giant cells. Blood vessels show prominent plump endothelial cells (1165,1887). Immunohistochemically the cellular infiltrate represents a mixture of polyclonal mature T- and B-lymphocytes (936).

**Inflammatory pseudotumour (IPT)** (plasma cell granuloma, inflammatory myofibroblastic pseudotumour) refers to a spectrum of idiopathic benign conditions with unknown etiology that can develop in various organs and deep tissues, particularly in the lung. Cutaneous IPT occurs as a solitary, slowly growing, tender nodule measuring 1-3 cm in diameter. Irrespective the anatomic location, the lesions share common histological features, showing well circumscribed proliferation of myofibroblasts/fibroblasts expressing smooth muscle actin (SMA) and vimentin, a mixed cell infiltrate containing high numbers of plasma cells with prominent germinal centres dispersed throughout the lesion. The plasma cells are polyclonal and are seen in the interfollicular areas (plasma cell granuloma) 21, (508,509). Later stages show marked fibrosis/sclerosis with thick collagen bundles arranged in concentric whorls.

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**Fig. 4.73** A Head of Ixodes ricinus fixed to the skin. B 1384. Borrelia burgdorferi in the dermis, silver stain.
Histological variations include presence of high endothelial venules, admixture of eosinophils, calcification, psammoma bodies, and presence of large polygonal myofibroblasts (vimentin+, CD15-, CD30-) (1476) with single, double or multiple nuclei and prominent eosinophilic nucleoli resembling Reed-Sternberg cells (388,1084,1476,1881,2561). Differential diagnosis of cutaneous IPT includes lymphoma, angiolymphoid hyperplasia with eosinophilia and Kimura and infectious dermatoses (mycobacteria, deep fungal infections). The later stages of cutaneous IPT should be distinguished from erythema elevatum diutinum, granuloma faciale and dermatofibroma with lymphoid infiltrate.

**Histogenesis**

Polyclonality is the hallmark of cutaneous pseudolymphomas. Besides T-cells and B-cells, mononuclear phagocytes represent a considerable proportion of the infiltrate. Eosinophils and polytypic plasma cells as well are present in most cases of either B-cell or T-cell pseudolymphomas of the skin (342).

**Somatic genetics**

No clonal rearrangement of T-cell receptor genes or of immunoglobulin heavy chain genes or light chain restriction of plasma cells is found.

**Prognosis and predictive factors**

The prognosis of cutaneous pseudolymphomas by definition is excellent, showing spontaneous regression of the lesions after cessation of the causative factor or due to treatment with non-aggressive treatment modalities. However there is a potential for some cutaneous pseudolymphomas to progress to cutaneous B-cell lymphoma (CBCL) (433,807,1339), or to cutaneous T-cell lymphoma (CTCL) (2545,2546).

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**PSL with mixed and unclassified infiltrates**

There are reactive lymphocytic infiltrates in the context of other skin disorders that can be referred to as pseudolymphomatous reactions in an even broader sense. Neoplasms, especially squamous cell carcinoma, basal cell carcinoma, and malignant melanoma, or naevi (halo [Sutton] naevi) may show a dense mononuclear infiltrate, composed of T cells or of B cells, sometimes with follicle formation, with polyclonal plasma cells being numerous especially in head and neck localizations.

---

**Fig. 4.74** Lymphadenosis benigna cutis (LABC, B-pseudolymphoma) following tick bite in the earlobe.

**Fig. 4.75** B-PSL. Reactive follicles in lymphadenosis benigna cutis (B-pseudolymphoma).

**Fig. 4.76** Close up view showing follicular centre with tingible-body macrophages featuring a starry sky pattern.

**Fig. 4.77 A** Tingible body macrophages containing ingested nuclear fragments. **B** Regular network of CD21+ dendritic cells.
Parapsoriasis

Definition
The term "parapsoriasis" is confusing. It encompasses a number of different pathologic states clinically manifested by chronic recalcitrant erythematous scaling skin lesions. Those diseases which have distinct clinical and histological changes do not fulfill criteria of malignancy, deserve to be labeled with a term which reflects this intermediate situation and labels them as distinct nosologic entities. This term since the days of Brocq has been "parapsoriasis" and there is no reason for changing it. Otherwise there will be a bias in epidemiologic data on frequencies, mortality rates and other parameters.

Two groups of parapsoriasis can be differentiated. The benign form ("parapsoriasis en plaques" [Brocq's disease]), which never evolves into malignant lymphoma and large plaque forms with or without poikiloderma which after several decades may evolve into mycosis fungoides or CTCL in up to 50% of the cases. Table 4.3 summarizes criteria for differentiation of benign and premalignant forms of parapsoriasis en plaques.

Small plaque parapsoriasis

Synonyms
Parapsoriasis, small patch (digitiform) type (Brocq's disease); Parapsoriasis en plaques, benign type; digitate dermatitis, xanthoerythrodermia perstans; chronic superficial dermatitis

Epidemiology
This form preferentially occurs in young adults and affects males more frequently than females. There are no statistically reliable data on the incidence, which is estimated less than 0.1 per 100,000 per year. There is little tendency to progress. Survival is not affected since SPP never evolves into malignant lymphoma

Clinical Features
Trunk and upper extremities are preferentially involved. Small (2-5cm in diameter), mostly oval or finger-like patches, slightly erythematous, following skin lines. The color is brown red, and fine and powdery (pityriasiform) scaling may be present. The surface is slightly wrinkled resulting in a pseudoatrophic appearance.

Histopathology
The epidermis is normal or slightly spongotic with patchy parakeratosis. Patchy loose perivascular and disseminated lymphocytic infiltrate, but no edema, are present in the dermis. Significant epidermotropism of lymphoid cells is lacking.

Immunohistochemistry
Lymphoid cells exhibit mostly CD4+ and some CD8+.

Somatic genetics
Clonal rearrangement for the T-cell receptor genes is not detectable. However clonal rearrangement of lymphoid cells in the peripheral blood of patients has been reported.

Prognosis and predictive factors
The skin lesions are extraordinarily stable in shape and size over years and decades without spreading to extracutaneous localizations. Lymph nodes, peripheral blood, bone marrow or internal organs are not affected. Life expectancy is normal. Progression into mycosis fungoides or other CTCL does not occur.

Fig. 4.78 Parapsoriasis. A Large plaque parapsoriasis with poikiloderma, showing large telangiectatic patches and a netlike pigmentation. B Flattening of the epidermal rete ridges. Band like lichenoid infiltrate. Dilated small blood vessels in the upper dermis.
Parapsoriasis - Large patch type, with or without poikiloderma

Definition
Pre-malignant inflammatory disorder with tendency to evolve into mycosis fungoides. Some authors consider this lesion a manifestation of early cutaneous T-cell lymphoma (CTCL).

Synonyms
Non-poikilodermatous variant. Parapsoriasis en plaques, premalignant type, parapsoriasis en grandes plaques simples. Poikilodermatous variant: Prereticulotic poikiloderma, parapsoriasis en grandes plaques poikilodermiques; poikiloderma vasculare atrophicans; parapsoriasis lichenoides; parakeratosis variegata.

Epidemiology
All age groups may be affected with a slight male preponderance.

Localization
Breast and buttocks are most commonly involved.

Clinical Features
Few large (more than 5 cm in diameter) patches showing pityriasiform scaling with (poikilodermatous variant), telangiectasia and netlike pigmentation are present. There is no palpable infiltration.

Tumour spread and staging
Lesions may stay unchanged over years and decades, or slowly show enlargement in a few cases. No plaques or tumours occur, except when the disease evolves into CTCL in some of the cases.

Histopathology
Under patchy parakeratosis there is slight atrophy of the epidermis, due to loss of rete ridges, in the poikilodermatous form. The subepidermal zone is free of lymphocytes, which accumulate in a band-like arrangement in the upper dermis, sparing the papillary region. There is no significant epidermotropism as usually seen in early stages of mycosis fungoides. The poikilodermatous variant of the disease in addition shows dilated blood vessels in the upper dermis.

Somatic genetics
T-cell receptor gamma gene rearrangement, which is clonal in about half of the patients with LPP, is probably without any prognostic significance (2186). Increased telomerase activity and shortened telomere length was also detected in CD4+ T cells from patients with parapsoriasis (2552).

Prognosis and predictive factors
There is no significant difference between the observed and expected survivals in patients with less than 10% skin involvement. (2575). However when skin involvement exceeds 10%, as seen in LPP, sporadic cases have an increased risk of transforming into mycosis fungoides after years or decades (2031).

<table>
<thead>
<tr>
<th>Table 4.03</th>
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<tbody>
<tr>
<td>Criteria for distinguishing benign and premalignant forms of parapsoriasis en plaques.</td>
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<tr>
<td></td>
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<tr>
<td>Age distribution</td>
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<tr>
<td>Sex incidence (m:f)</td>
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<tr>
<td>Clinical features</td>
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<tr>
<td>Preferential localizations</td>
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<tr>
<td>Histological features</td>
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<tr>
<td>Prognosis</td>
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</tbody>
</table>

216 Haematolymphoid tumours
Langerhans cell histiocytosis

Definition
Langerhans cell histiocytosis (LCH) is a clonal disorder with systemic spread, characterized by proliferation of dendritic cells which bear morphologic and phenotypic markers of Langerhans cells, characterized by Birbeck granules and expression of CD1a and S-100.

ICD-O code 9751/1

Synonyms
Histiocytosis-X, Langerhans cell granulomatosis, Langerhans cell disease

Epidemiology
LCH predominantly occurs in infants. Median age at diagnosis is 3-5 years (2,299). It has also been reported in patients up to the ninth decade of life (1551,1578,1941), and occurs equally in men and women. The incidence has been estimated as 0.1–0.5 per 100,000 population per year. There have been reports on familiar cases with autosomal recessive inheritance.

Etiology
The etiology is unknown. Different groups have studied female patients with cutaneous LCH using a variety of x-linked polymorphisms to demonstrate clonality (2530,2574). In some cases, association with lymphomas, leukaemias and lung tumours (666) has been observed; in others, infections and environmental factors, including El Nino, have been related to childhood LCH (455). Many view LCH as a reactive process (716,2583) because of its tendency toward spontaneous remission and response to mild, non-toxic therapy.

Localization
Two thirds of the sites of involvement diagnosed throughout the course of the disease are present at diagnosis (2). Initial bone involvement is found in almost all patients. Other organs involved skin (25-100%, depending on subtype), ear, liver, lung, and lymph nodes (299).

Clinical Features
The clinical presentation of LCH is very diverse and depends on the subtype. Skin lesions may be seen either as single organ involvement or as part of a multorgan systemic disease in 25-100% of cases. Any anatomic site can be involved including scalp, nails, palms and soles as well as mucous membranes.

Letterer-Siwe Disease
This is the most severe, disseminated form of Langerhans cell histiocytosis. It affects children in their first year of life but occurrence in adults has been reported (1731). Tiny (0.5 mm in diameter) rose-yellow or brownish-red, translucent papules and patches are found on the scalp, diaper and seborrhoeic sites like nasolabial folds, perioral region, and on the upper trunk. In time, the papules become scaly and crusted and may coalesce into plaques. Petechial and purpuric lesions, pustules and vesicles as

Table 4.04
Langerhans cell histiocytes and their characteristics. This classification has limitations because of the highly variable manifestations of the disease with many overlapping features (340).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age</th>
<th>Skin involvement</th>
<th>Clinical Features</th>
<th>Course</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letterer Siwe</td>
<td>First years of life</td>
<td>~90-100%</td>
<td>Fever, weight loss, lymphadenopathy, hepatosplenomegaly, pancytopenia, bone lesions</td>
<td>Acute</td>
<td>Mortality rate: 50-66%</td>
</tr>
<tr>
<td>Hand-Schüller Christian</td>
<td>Children adults</td>
<td>~30%</td>
<td>Osteolytic bone lesions, diabetes insipidus, exophthalmos, otitis</td>
<td>Subacute to chronic</td>
<td>Mortality rate: &lt;50%</td>
</tr>
<tr>
<td>Eosinophilic granuloma</td>
<td>Mainly adults</td>
<td>&lt;10%</td>
<td>Solitary bone or skin lesions</td>
<td>Chronic</td>
<td>Favorable</td>
</tr>
<tr>
<td>Congenital self-healing reticulohistiocytosis (CSHR)</td>
<td>Congenital</td>
<td>100%</td>
<td>Skin lesions only</td>
<td>Self healing</td>
<td>Excellent*</td>
</tr>
</tbody>
</table>

*Both relapses and conversion to systemic disease can occur, so long-term follow-up is needed (3369).
well as small erosions can also be seen. Nodules are uncommon, but may be found on the trunk and tend to ulcerate. Additional symptoms include fever, weight loss, rash, lymphadenopathy, hepatosplenomegaly, pancytopenia and purpura.

**Hand – Schüller - Christian disease**
The typical triad includes osteolytic skull lesions (100%), hypopituitarism induced diabetes insipidus (50%), and exophthalmos (10%). Otitis media, generalized lymphoadenopathy, hepatosplenomegaly, and pulmonary disease may be additional findings. Skin lesions occur in about 30% of cases, usually in the intertriginous areas, most often as papules and nodules which may be ulcerated, erosive and superinfected.

**Eosinophilic granuloma**
The most common site of involvement is bone. The uncommon cutaneous lesions are deep dermal or subcutaneous nodules which are not clinically distinct (818,1956). Lesions have to be differentiated from granuloma eosinophilicum faciei, a chronic variant of leukocytoclastic vasculitis with variable presence of eosinophils, but usually no extracutaneous manifestation (452).

**Congenital self-healing reticulo-histiocytosis (CSHRH)**
CSHRH (synonyms: Hashimoto-Pritzker disease; congenital reticulohistiocytosis; congenital self-healing Langerhans cell histiocytosis) (981,2082) is a rare condition (5% of all LCH), initially seen at birth or in the neonatal period, with solitary, localized to generalized papules, vesicles, or nodules on the trunk, head, palms and soles, sometimes showing central ulceration (217). The skin lesions tend to involute spontaneously within weeks to months leaving behind hypo- or hyperpigmented macules or patches (979,1372). Affected infants are otherwise well (1369). Patients should be carefully followed since relapses may occur, including bone involvement, and the occasional case may progress to Letterer-Siwe disease (1445). Some cases of CSHRH may be clinically confused with the blueberry muffin syndrome, congenital leukaemic infiltrates, xanthogranulomas or mast cell disease, but the microscopic picture brings clarity (360).

**Histopathology**
The hallmark and unifying feature of all variants of LCH is a cell with large, pale, folded or lobulated, often reniform, vesic-
ular nucleus and abundant, slightly eosinophilic or amphophilic cytoplasm. Nucleoli are not prominent. Histological variations correlate with the clinical appearance of the lesions. Features may be predominantly proliferative in Letterer-Siwe disease, xanthomatous in Hand-Schüller-Christian-disease, granulomatous as in eosinophilic granuloma, or “reticulocytic” with abundant eosinophilic cytoplasm (ground glass appearance of giant cells) in Hashimoto-Pritzker disease. Fully developed papules and plaques show a dense band-like infiltrate obscuring the dermo-epidermal junction. Epidermotropism of LCs with intraepidermal microabscess formation can be found. In addition to LCs and eosinophils, the infiltrate may contain variable numbers of lymphocytes, epithelioid macrophages including foam cells and giant cells, neutrophils, plasma cells, and extravasated erythrocytes.

Immunohistochemistry
The phenotypic hallmarks in LCH are expression of CD1a, CD4 and S-100 protein, while macrophage markers, including CD68 and lysozyme, are usually negative.

Electron microscopy
Rod- or rocket-shaped granules measuring 200-400 nm (Birbeck granules, Langerhans cell granules) are the ultrastructural hallmark of LCs. The number of Birbeck granules varies, with usually greater prominence in early lesions. Coexistence of myelinoid laminated inclusions or “vermiform” bodies (1372) and Birbeck granules is common in CSHRH.

Genetics
A variety of inconsistent cytogenetic abnormalities have been found in several patients with LCH studied so far using comparative genomic hybridization, loss of heterozygosity (LOH) and other techniques (107,227,848,1666). Heterogeneous overexpression of TGFbeta receptor I and II, MDM2, p53, p21, p16, Rb, and BCL2 has been detected in lesional LCH cells (2097). Familial clustering of two different manifestations of LCH support a role for genetic factor(s) in LCH and raise the possibility of inherited mutations that promote emergence of clonal Langerhans cells (93,134,1200). LCH may follow precursor T-cell acute lymphoblastic leukaemia, and in such cases a clonal relationship has been shown for T-cell receptor gene rearrangements (720).

Prognosis and predictive factors
The biologic behaviour of LCH ranges from spontaneous remission to lethal dissemination, and such behaviour cannot be predicted on the basis of histologic features (1941). The presence and degree of organ dysfunction, age less than 1 year at diagnosis (except the Hashimoto-Pritzker type), male sex, progressive episodes, and the absence of response to therapy are the most reliable indicators of prognosis (2,1019). In general, about 10% of patients with multifocal disease die, 30% undergo complete remission, and the remaining 60% embark upon a chronic course (1065, 1425).
**Indeterminate cell histiocytosis**

**Definition**
Indeterminate cell histiocytosis (ICH) is a proliferative cutaneous disorder of the so-called “indeterminate cells” (IC), i.e. distinct dendritic cells of the skin that display histological, ultrastructural and antigenic features similar to those of Langerhans cells, but do not contain Birbeck granules.

**Epidemiology**
The disease is very rare (about 15 cases described up to 2003), usually occurs during adulthood, although two cases were in teenagers (1621,2019) and two cases in children (1413,1524). Both sexes have been affected.

**Etiology**
The origin of indeterminate cells is still debated. Indeterminate cells may derivate from an arrest of Langerhans cell migration and maturation (1302), may represent precursors of Langerhans cells which acquire Birbeck granules as they transit from dermal to epidermal sites (1499). Furthermore it has been suggested (222) that indeterminate cells represent members of the epidermal/dermal dendritic cell system which migrate from skin to regional lymph nodes. According to this concept, indeterminate cell histiocytosis can be considered a disorder due to locally arrested dermal indeterminate cells proliferating prior to their departure for lymph nodes.

**Localization**
Lesions are usually restricted to the skin. Solitary lesions have been described on the trunk and arms, while multiple lesions are widespread.

**Clinical features**
The eruption consists of a solitary nodular lesion (222,279,1413,1621) or of multiple papulonodules (279,531,1499,2019,2179). Solitary nodules are soft, red in colour and about 1 cm in diameter, and may be ulcerated. Multiple lesions are firm, asymptomatic papulonodules ranging in size from a few millimetres to 1 cm, varying in colour from dark-red to brownish, and covered by intact skin. These lesions appear in successive crops. Mucous membranes are always spared. Visceral involvement has been observed only in a child. Patients are in good general health.

**Histopathology**
Light-microscopic evaluation reveals an infiltration of histiocytic cells in the whole dermis and sometimes within the epidermis. The proliferating cells show an abundant pale eosinophilic cytoplasm and large irregular folded or twisted nuclei. A few mitotic figures and multinucleated giant cells may be observed. Clusters of lymphocytes are admixed.

**Immunohistochemistry**
Proliferating cells are weakly positive for CD1a, CD68 (KP1), CD11c (Leu M5), CD14 (OKM1), factor XIIIa, lysozyme, α1-antitrypsin, HLA-DR, but negative for CD207 (langerin) (1302,1499,1524,1621,2179).

**Electron microscopy**
The proliferating cells reveal an indented nucleus and an abundant cytoplasm with lysosomes, phagosomes and a well-developed endoplasmic reticulum. Birbeck granules are absent (222,531,1413).

**Prognosis and predictive factors**
Most cases have exhibited complete or partial spontaneous regression of lesions without recurrences. Two cases displayed malignant behaviour (279,1524). The prognosis is reasonably good, but leukaemia may be associated with this disease (279,1302).

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**Fig. 4.83** Indeterminate cell histiocytosis. Multiple firm, asymptomatic papulonodules on the trunk, ranging in size from few millimetres to 1 cm, varying in colour from dark red to brownish.

**Fig. 4.84** Indeterminate cell histiocytosis. The proliferating cells show an irregular, often reniform, vesicular nucleus, surrounded by abundant pale cytoplasm. From: R. Caputo (378).

**Fig. 4.85** The proliferating cells reveal an indented nucleus and an abundant cytoplasm with lysosomes, phagosomes and a well-developed endoplasmic reticulum. Birbeck granules are absent.
Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)

Definition
Sinus histiocytosis with massive lymphadenopathy is a reactive condition of unknown etiology, characterized by a poliiferation of histiocytes which usually exhibit emperipolesis of lymphocytes. The disease can mimic lymphoma. Extranodal involvement is frequent.

Synonyms
Sinus histiocytosis with massive lymphadenopathy, Rosai-Dorfman disease

Epidemiology
Sinus histiocytosis is a rare non-neoplastic disease. Lymph nodes are predominantly affected in children and young male adults; the cutaneous form is particularly seen during the third and fourth decades in female patients (74,307,483).

Etiology
The etiology is unknown. Lesions are polyclonal, probably the consequence of a cytokine dysregulation (1603).

Localization
Cervical lymph node involvement is most characteristic. Cutaneous lesions frequently occur on the head and neck, mucous lesions (1105,2498) in the nose and paranasal sinus. Extranodal disease may also affect any other organ (2455).

Clinical features
Children with massive cervical lymph node swellings frequently suffer from fever and malaise. Laboratory tests show leukocytosis, anemia, polyclonal hyper-gammaglobulinaemia and an accelerated erythrocyte sedimentation rate. Extranodal involvement is common, up to 40%. Pure cutaneous forms are rare; solitary, clustered or wide-spread, red to brownish papules, rarely plaques and nodules are seen. Regression leaves atrophic, brown macules.

Histopathology
Lymph node architecture is replaced by sheets of faintly stained (“clear”) to slightly eosinophilic macrophages. In extranodal location infiltrates frequently simulate lymph node sinuses (“sinusoidal pattern”). Emperipolesis of lymphocytes, erythrocytes or other nuclear debris is prominent, but not specific; it can also be seen in, e.g., subcutaneous T-cell lymphomas. Lymphocytes, plasma cells, neutrophils and fibrosclerosis are found to a variable degree.

Immunohistochemistry
Macrophages are positive for CD68 (PGM1, KP1) and S100 protein; CD1a, factor XIIIa and CD34 are negative (1796).

Electron microscopy
Macrophages ingest intact lymphocytes. Phagolysosomal structures, but no Birbeck granules are found.

Prognosis and predictive factors
Manifestation in children and lymph node involvement are more readily and rapidly associated with regression than in adults and spread to extranodal sites. The vast majority of lesions is self-limited and benign. Rare fatalities have been associated with immunologic disorders, lymphomas of Hodgkin and non-Hodgkin type, leukaemias (62), and exceptional cases with solid tumours (1900).

Fig. 4.86 Sinus histiocytosis with massive lymphadenopathy. A Left: Brownish nodule of sinus histiocytosis on the nose. Right: Clustered brownish papules of sinus histiocytosis on the trunk. B Left: Sheets of macrophages in sinus histiocytosis positive for S100 protein. Right: Lymphocytes within cytoplasm of histiocytes, i.e., emperipolesis.
**Definition**

Juvenile xanthogranuloma (JXG) is a benign, self-healing, non-Langerhans-cell (LC) histiocytosis most frequently seen in infants and children, characterized by yellowish asymptomatic papules and/or nodules located in the skin and other organs and consisting of an infiltrate of macrophages with a variable degree of lipidization in the absence of a metabolic disorder.

**Synonyms**

Xanthoma multiplex [33]; Nevocantho-endothelioma [1551].

**Epidemiology**

JXG is the most common form of non LC histiocytosis [378,824]. JXG appears within the first year of life in about 75% of cases; in 15-30% it is present at birth.

**Etiology**

The etiology is unknown. Foamy cells constitute the main part of the mature lesions of JXG and accumulate lipids, despite normal levels of plasma lipids. It has been suggested [208] that the uptake of low-density lipoprotein cholesterol and the biosynthesis of intracellular cholesterol are both enhanced; such enhancement might play a role in the process of accumulation of cholesterol esters in the macrophage.

**Localization**

Cutaneous lesions are irregularly scattered throughout the skin without a tendency to cluster, and are mainly located on the upper part of the body [378,824]. Mucous membranes may rarely be involved.

The most common extracutaneous manifestation of JXG (occurring mainly in the papular and subcutaneous [256] forms) is ocular involvement [256,614,2045, 2603]. Ocular lesions may occur in about 1-10% of affected children and are almost always unilateral and may lead to haemorrhage and glaucoma. Such lesions may precede or follow the cutaneous lesions. The nodular variant of JXG may occasionally be related to systemic lesions of lungs, bones, kidneys, pericardium, colon, ovaries, testes and central nervous system [378,824,2536].

**Clinical features**

Two main clinical variants can be distinguished: a papular form and a nodular form [824]. The papular form is the most frequent and is characterized by numerous (up to 100), firm hemispheric lesions, 2-5 mm in diameter, that are red-brown at first and then quickly turn yellowish. These lesions are associated in perhaps 20% of patients with café-au-lait spots of neurofibromatosis (1140) and may be related to juvenile chronic myeloid leukaemia (538,1650). The nodular form is less frequent, and is marked by one or a few lesions. The nodules are round to oval, 1-2 cm in diameter, high-domed, shiny, translucent, yellowish or red brown and sometimes show telangetasias on their surface. The term giant JXG has been used to indicate lesions larger than 2 cm. Unusual clinical variants [378,383] are the mixed form (simultaneous presence of both papules and nodules) and the form en plaque, a group of JXG lesions with a tendency to coalesce into a plaque as the only expression of the disease.

**Histopathology**

Early lesions are characterized by a dense infiltrate of monomorphous, non-lipid containing, macrophages with abundant, slightly eosinophilic, cytoplasm [378,824]. With time the cytoplasm of macrophages becomes laden with lipid and appears foamy. Mature lesions contain foamy cells, for-
eign body giant cells and Touton giant cells, mainly distributed in the superficial dermis and on the border of the infiltrate. In addition to macrophages and foamy cells, there may be lymphocytes, eosinophils, neutrophils and plasma cells scattered throughout the lesion. In older lesions fibrosis replaces the cellular infiltrate, and lipids are not present extracellularly.

**Immunohistochemistry**

Immunohistochemically \( \{824,2049\} \) macrophages and Touton cells show a uniform positive staining with CD14, CD68, HAM56 (markers with specificity for macrophages) and vimentin, frequent positive staining for factor XIII (markers of dermal dendrocytes) and for cathepsin B and occasional staining for MAC387 (a marker for monocytes and macrophages). S100 protein, CD1a (OKT6), CD15 (Leu M1) and peanut agglutinin (PNA) are not usually expressed on the macrophages of JXG.

**Genetics**

JXG is not linked to any genetic locus, but the association with café-au-lait spots of neurofibromatosis (NF1) \( \{2536\} \) and the occasional association with neurilemmomatosis (NF2) \( \{1115\} \) suggests that a JXG locus could reside on chromosome 17q11.2 or 22q12. Clinical \( \{1115\} \) and genetic analyses \( \{1056\} \) indicate that neurilemmomatosis and neurofibromatosis type 2 (NF2) genes are identical.

**Prognosis and predictive factors**

The papules and nodules of the skin tend to flatten with time and both the skin and most of the visceral lesions disappear spontaneously within 3-6 years. A few cases of JXG with fatal evolution, probably due to central nervous system involvement \( \{378\} \) or fatal liver disease \( \{614\} \), have been reported. In JXG periodic complete blood count and peripheral smears would be judicious during a patient's first two years of life, which is the time of the peak incidence for juvenile chronic myeloid leukaemia.
Reticulohistiocytosis

Definition
Reticulohistiocytosis of the skin represents a spectrum of rare clinical entities, ranging from the solitary cutaneous form (SCR) through the generalized cutaneous form without systemic involvement (GCR), to multicentric reticulohistiocytosis with systemic involvement (MR). The skin lesions in all these conditions demonstrate an identical histological pattern, characterized by numerous mononucleated or multinucleated macrophages with abundant, eosinophilic, homogeneous to finely granular cytoplasm with a characteristic ground-glass appearance.

Synonyms
Giant cell reticulohistiocytosis, giant cell histiocytosis; cutaneous reticulohistiocytoma, reticulomatosis with giant cell histiocytes; normocholesterolemic xanthomatosis; lipid dermatitis; lipid rheumatism; multicentric reticulohistiocytosis; non-diabetic cutaneous xanthomatosis; reticulohistiocytic granuloma; reticulohistiocytosis of the skin and synovia.

Epidemiology
Reticulohistiocytosis mostly occurs in adults over 40 years of age, but the disease may appear during adolescence: SCR and GCR have been also observed in children. In adults, the most frequent variant is MR, with about 50 and GCR with 10 patients reported in the literature. There is no preference for either sex (167,465,1405,1462).

Etiology
The etiopathogenesis is unknown. Reticulohistiocytosis may represent an abnormal macrophage response to different stimuli. In solitary forms, local trauma such as insect bites, folliculitis or ruptured infundibular cysts may play a role (379), while in systemic forms the association with autoimmune disorders and internal malignancies suggests an immunological basis for the initiation of this reaction (1752).

Localization
SCR involves mainly the head and the neck, but may be found in any cutaneous site (382,1082). In GCR the lesions are widely scattered on the skin (381,547,847,2363). In MR (167,413,465,1405,1752) skin lesions preferentially affect the fingers, the palms and the back of the hands, the juxta-articular regions of the limbs and the face. Oral, nasal and pharyngeal mucosa are involved in 50% of cases. Osteoarticular lesions involve mainly the hands (80%), knee (70%) and wrists (65%).

Clinical features
The solitary cutaneous reticulohistiocytosis (SCR) or reticulohistiocytoma cutis (382,1082) is characterized by a single, firm, rapidly growing nodule varying in colour from yellow-brown to dark-red. The lesion is often clinically misdiagnosed, it occurs without evidence of systemic involvement, and its onset may be preceded by trauma. Generalized cutaneous histiocytosis (GCR) (381,547,847,2363) is a purely cutaneous form characterized by the eruption of firm, smooth, asymptomatic papulonodular lesions, 3-10 mm in diameter. The colour of the recent lesions is pink-yellow, while the older lesions show a red-brown colour. Joint and visceral lesions are absent. Possibly, this purely cutaneous form could represent an early stage of multicentric reticulohistiocytosis, before the appearance of joint or visceral lesions.

The term multicentric reticulohistiocytosis (167,413,465,1405,1752) is used to indicate a form of reticulohistiocytosis characterized by the association of a cutaneous and mucous membrane papulonodular eruption with severe arthropathy and other visceral symptoms. The papulonodular lesions range in diameter from a few mm to 2 cm, and are round, translucent and yellow-rose or yellow-brown in colour. Grouping of lesions into plaques can give a cobblestone appearance, but lesions are mostly scattered and isolated. They do not tend to ulcerate, and are pruritic in about one-third of cases. Osteoarticular manifestations cause severe chronic polyarthritis with arthralgias, and are the initial sign of the disease in about 5-65% of cases (167,465,1405). The osteoarticular lesions

Fig. 4.91 Multicentric reticulohistiocytosis. A Purplish-brown, firm nodules characteristically affect the fingers. Periungual papules are arranged about the nail folds. B Papulonodular lesions are spread on the face, lips and oral mucosa. Mucous membranes are involved in about 50% of cases. C Symmetrical involvement of the knees. In this patient, osteoarticular manifestations were the initial sign of the disease. From: R. Caputo (378)
show a progressive destructive course of 6-8 years, and then become stable. Other systemic localizations, histopathologically documented, are very rare. Muscular (667) (myositis, myotonia and myoarthrophy), cardiopulmonary (532) (pericarditis, cardiac insufficiency, pleuritis, pulmonary infiltration), ocular (667) (exophthalmos, conjunctival infiltration), gastric (gastric ulcer), thyroid (thyroid nodules) and submandibular salivary gland involvements have occasionally been reported. Fever, weight loss and weakness can be present. In MR there is an association with a variety of autoimmune disorders such as dermatomyositis, lupus erythematosus, or Hashimoto thyroiditis as well as internal malignancies in 15-27% of cases (167,413,1405,1752). Solid tumours such as bronchial, breast, stomach and cervical carcinomas are most common. Lymphomas and myelodysplastic syndromes have been found less frequently.

**Histopathology**

The histological findings in the three types of reticulo-histiocytosis and in the different tissues are identical (167,465,1405,1462). Early lesions are composed of macrophages and lymphocytes, and therefore may be confused with other histiocytoses of the skin. Older lesions show the characteristic histological pattern: the presence of numerous large, mononuclear or multinucleated macrophages with an abundance of eosinophilic, homogeneous to finely granular cytoplasm having a ground glass appearance. At times, phagocytosis of connective tissue and/or cellular components may be seen (379,532). Histochemically, the granular material in macrophages and giant cells stains with periodic acid-Schiff, Sudan black and scarlet red, indicating the presence of glycolipids and/or glycoproteins and neutral fat (167).

**Immunohistochemistry**

Macrophages stain with macrophage markers KP1/PGM1 (CD68), Ki-M1p, and for the mesenchymal epitope of vimentin, and show variable reactivity with HAM56 and for factor XIIa, lysozyme and α1-antitrypsin (381,382,424,2027,2585). In contrast, these cells are usually negative for CD1α, S100 protein, Leu-M1 (CD15) and MAC387. Rare exceptions have been reported. According to Zelger et al. (2585), SCR differs histopathologically and immunohistochemically from MR as lesions are better circumscribed, multinucleated giant cells more prominent, gigantic and bizarre, and macrophages regularly negative for factor XIIa in the former entity.

**Electron microscopy**

The infiltrate is formed by large mononuclear to multinucleated cells exhibiting numerous peripheral villi (532,667). Nuclei are irregular and often polylobated, with nucleoplasm of medium electron density and one or two nucleoli. The cytoplasm contains one or more Golgi apparatus, and is rich in mitochondria, lysosomes, dense bodies, phagosomes and myelin figures. The cytoplasm of about 5-40% of the cells of the infiltrate in many cases contains the so-called pleomorphic cytoplasmic inclusions (380-382,532), varying in number from cell to cell. The pleomorphic cytoplasmic inclusions are unique and highly complex structures consisting mainly of unit membranes, occasionally surrounding electron-dense areas containing vesicles. Birbeck granules are absent. About 20% of all macrophages show collagenophagic activity (379,766), but not pleomorphic cytoplasmic inclusions.

**Prognosis and predictive factors**

The purely cutaneous forms of reticulo-histiocytosis (solitary and generalized) may involute spontaneously (382,847). It is possible that the generalized purely cutaneous form is an early stage of MR, before the appearance of joint and visceral lesions (381,847). In MR, there is no parallelism between the mucocutaneous and articular manifestations. The mucocutaneous lesions have an unpredictable course, and may remit spontaneously. In half of the patients, the osteoarticular manifestations become stable, while in the other half, they show a progressive destructive course (1405). The prognosis is favourable for the cutaneous forms. The prognosis of MR is related to the importance of the osteoarticular manifestations and of the underlying immunologic disorders and neoplasms.

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**Fig. 4.92** Reticulohistiocytosis. A Conventional microscopy: the histological pattern of the lesions is characterized by the presence of numerous, large, mononucleated histiocytes with an abundant eosinophilic, finely granular cytoplasm. B Conventional microscopy: in these giant cells showing leukocyte phagocytosis, the typical ground-glass appearance of the cytoplasm is evident. C Conventional microscopy: Weigert-Van Gieson staining. Collagen phagocytosis is an occasional finding.

**Fig. 4.93** Reticulohistiocytosis. Electron microscopy: the polymorphism of the granules is evident at higher magnification.
Mastocytosis

Definition
Mastocytosis is a heterogeneous group of disorders characterized by the abnormal growth and accumulation of a clone of mast cells in one or more organ system (1448). Most patients have cutaneous mastocytosis (CM) with indolent disease that is confined to the skin and that may regress spontaneously. A minority of patients, usually adults, have systemic mastocytosis (SM) that may rarely be highly aggressive and associated with multi-system involvement and short survival time, or that may be associated with non-mast-cell haematopoietic malignancies (1450, 2372,2405).

ICD-O Codes
Cutaneous mastocytosis (CM); maculopapular or plaque type mastocytosis, formerly urticaria pigmentosa (UP); telangiectatic mastocytosis, formerly telangiectasia macularis eruptiva perstans (TMEP); diffuse cutaneous mastocytosis (DCL); solitary mastocytoma (965,2405)
Indolent systemic mastocytosis 9740/1
Aggressive systemic mastocytosis 9741/1
Mastocytosis with associated haematopoietic disorder 9741/3
Mast cell leukaemia 9742/3

Synonyms
Mast cell disease; mast cell proliferative disease

Epidemiology
Cutaneous mastocytosis may be present at birth and usually first appears before six months of age. A second peak incidence is found in young adults in their 3rd and 4th decades. Paediatric mastocytosis usually regresses by adolescence. Adult mastocytosis is more likely to be persistent and may be associated with SM, rarely also with aggressive systemic mastocytosis. There is no clear gender or ethnic predominance of cases (964,1450).

Etiology
The KIT protein is a receptor tyrosine kinase that is also known as the mast cell growth factor receptor. Adult mastocytosis and rare pediatric cases are associated with somatic mutations in the c-KIT proto-oncogene that alter the enzymatic site of the KIT protein (361,1449). Rare kindreds with familial mastocytosis have germ line c-KIT mutations that affect regulatory portions of the KIT protein, also causing constitutive kinase activation. These patients may also have gastrointestinal stromal tumours (GISTs) which are known to be caused by regulatory type c-KIT activating mutations (189,
Patients with extensive involvement may present with tachycardia, and respiratory symptoms. Hypertension including anaphylaxis, syncope, headache, seizures, hypertension including anaphylaxis, tachycardia, and respiratory symptoms. These symptoms can affect the cardiovascular system (flushing, cramping) or the cardio-pulmonary system (tachycardia, hypotension). Organs or due to release of mast cell mediators into the circulation. Organs or due to mast cell infiltration of specific tissues. Accumulation of edema fluid results in grossly evident, widespread doughy dermal thickening with accentuation of cutaneous surface markings, giving a so-called “peau d’orange” appearance. Tense blisters filled with clear fluid, occasionally slightly-tinged with blood, may be seen overlying lesions of any form of cutaneous mastocytosis in infants.

Individual lesions in young children tend to be lightly pigmented and macular, rather than macular lesions and for larger, lightly pigmented patches with telangiectasias that may rarely occur in adults. Cutaneous involvement in SM usually appears morphologically identical to CM in adults, but may also show larger plaque-like lesions.

Histopathology
In haematoxylin and eosin (H&E) stained sections, normal mast cells have moderately abundant, oval or polygonal shaped cytoplasm with round to oval nuclei. The nuclei have clumped chromatin and indistinct or inapparent nucleoli. The cytoplasms are metachromatically purple.

**Fig. 4.95** Mastocytoma of the skin. Stains containing toluidine blue stain the mast cell cytoplasmic granules metachromatically purple.

Clinical features
Cutaneous mastocytosis includes several distinct clinicopathologic entities whose morphologies include solitary tumours (Mastocytoma), maculo-papular or plaque-type lesions that are mostly symmetrically distributed (UP/TMEP), and diffuse cutaneous involvement (DCM).

Stroking of any lesion of CM may cause mast cell degranulation with localized swelling or urtication (Darier sign). Clinically normal skin may also urticate when stroked, (so-called dermographism). Moderate itching is present in about half of the patients. Most cutaneous lesions show an increase in epidermal melanin pigment which, combined with the tendency of these lesions to urticate, has led to the term “urticaria pigmentosa”, a historic designation that has recently been proposed to be abandoned. Blistering or bullous mastocytosis is not a distinct entity but represents an exaggeration of Darier sign seen in infants whose dermo-epidermal junction is not well developed so that accumulation of edema fluid results in the formation of localized blisters. Other symptoms of mastocytosis may be due to mast cell infiltration of specific organs or due to release of mast cell mediators into the circulation. Organs affected include: the gastrointestinal tract (peptic ulcer disease, diarrhoea and cramping) or the cardio-pulmonary and cardio-vascular systems (flushing, syncope, headache, seizures, hypertension, hypotension including anaphylaxis, tachycardia, and respiratory symptoms). Patients with extensive involvement may have relatively vague constitutional symptoms including fatigue, weight loss, fever, sweats, and non-specific psychiatric symptoms. Patients with SM may have also bone-related complaints such as pain, fractures, or arthralgias, secondary to direct mass effects or generalized osteoporosis.

The diagnosis of cutaneous mastocytosis is established by skin biopsy that demonstrates increased numbers of mast cells in the dermis. Imaging studies or biopsy of bone marrow or other internal organs are usually not indicated in the absence of abnormality of the peripheral blood counts or specific signs or symptoms pointing to internal organ involvement.

The clinical presentation of CM may range from subtle diffuse erythema to grossly evident, widespread doughy dermal thickening with accentuation of cutaneous surface markings, giving a so-called “peau d’orange” appearance. Tense blisters filled with clear fluid, occasionally slightly-tinged with blood, may be seen overlying lesions of any form of cutaneous mastocytosis in infants. Individual lesions in young children tend to be lightly pigmented and occur as solitary nodules or multiple papules, or rarely as large heavily pigmented macules, large plaques, or diffuse infiltration of the skin. Large lesions or diffuse involvement in children may point to the presence of c-KIT activating mutations. In adolescents and adults, the individual lesions tend to be more heavily pigmented and macular, rather than papular, like those of young children. The term TMEP has been used for these macular lesions and for larger, lightly pigmented patches with telangiectasias that may rarely occur in adults. Cutaneous involvement in SM usually appears morphologically identical to CM in adults, but may also show larger plaque-like lesions.
Haematolymphoid tumours

...ficial dermis, within the dermal papillae (1401,1607). In solitary mastocytomas and papular, nodular, or diffuse CM, the papillary and/or reticular dermis may show either scanty increases in mast cell numbers or heavy mast cell infiltrates, and there may be extension into the subcutaneous fat. In CM, individual mast cells may rarely be found in the lower epidermis. Unequivocal diagnosis of cutaneous mastocytosis requires the demonstration of aggregates of mast cells within the dermis, and this may be difficult and require multiple biopsies in the TMEP form of adult mastocytosis. Lesions of mastocytosis are usually composed of an infiltrate of monomorphous mast cells, and rarely observed infiltrating eosinophils should raise the possibility of dermal hypersensitivity reaction, parasitosis or an arthropod bite.

Histogenesis
Mast cells are derived from CD34+ haematopoetic precursor cells (1982).

Somatic genetics
Mastocytosis is a clonal disease in both adults and children (1448,1449). The tumour cells of almost all cases of adult onset sporadic disease carry somatic point mutations of c-KIT that change the enzymatic site of the KIT protein, causing constitutive activation (361,1449). Paediatric sporadic mastocytosis has also been shown to be clonal, but c-KIT activating mutations are rare (361,1449). Very rare cases of familial mastocytosis, usually associated with GISTs tumours, are associated with germ line c-KIT mutations that activate KIT by affecting regulatory portions of the molecule, rather than the enzymatic site (189, 1447).

Prognosis and predictive factors
Patients with mastocytosis confined to the skin generally have a good prognosis, and cutaneous involvement is usually an indicator of a relatively better prognosis in SM. CM in paediatric patients with solitary mastocytomas or typical papular and macular rashes usually regress by adolescence. The presence of enzymatic site type KIT activating mutations may indicate persistent disease in this population, and classification of mastocytosis based on both clinical and molecular genetic features may eventually prove to be both prognostically and therapeutically useful (1446, 1465). In adults, although CM may be symptomatic and persist, overall survival is usually not adversely affected, even in the face of concomitant systemic involvement. Patients having aggressive variants of SM, however, may have a rapidly progressive downhill course with survival measured in months. In patients with associated haematologic malignancies, the prognosis is determined by the course of the related haematologic disease (964).