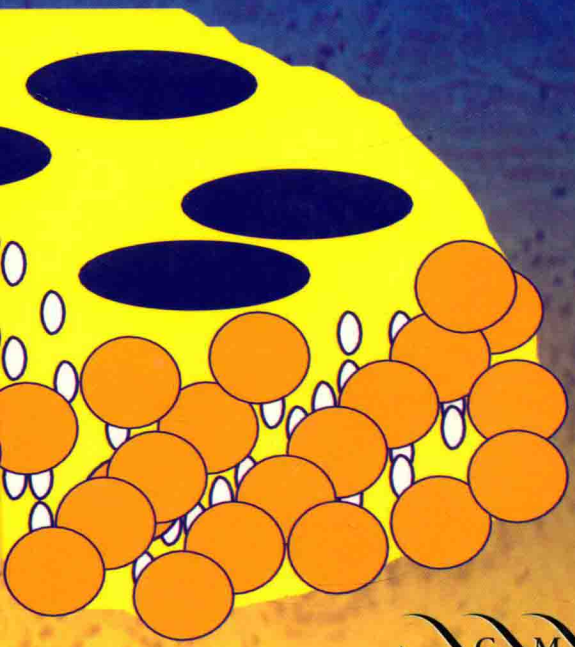
Progress in Pathology

Volume 5

Edited by

Nigel Kirkham

Nicholas R. Lemoine



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LONDON SAN FRANCISCO

Greenwich Medical Media Limited
137 Euston Road
London
NW1 2AA

870 Market Street, Ste 720
San Francisco
CA 94109

ISBN 1 8411 00 501

First published 2001

A catalogue record for this book is available from the British Library.

Distributed worldwide by Plymbridge Distributors Ltd
and in the USA by Jamco Distribution

Typeset by Saxon Graphics Ltd, Derby
Printed in China

Visit our website at:
www.greenwich-medical.co.uk

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Preface

Volume 5 of *Progress in Pathology* sees us with a new publisher, but the formula remains the same. We aim to bring you a collection of interesting, thought provoking and useful chapters. In this volume we have three chapters on difficult areas in dermatopathology as well as a timely review on the sentinel node biopsy: a procedure that is likely to become very widely used in the near future, especially if its value is supported by the clinical trials currently under way.

Other contributions cover aspects Barratt's oesophagus and the routine reporting of non-neoplastic gastric biopsies. The potentially useful technique of X-ray micro-computed tomography is described. The molecular basis of inherited skin disorders is reviewed and put into its clinical context. The importance of arterial remodelling is reviewed. The volume concludes with discussions of how errors may occur in histopathology and of aspects of the mathematical basis of diagnosis.

We feel confident that this volume will make a good read and a useful reference. We look forward to bringing the next volume to you when we will all be established in the third millenium.

Brighton N.K.
London N.R.L.
2001

Contents

1

The clinicopathological spectrum of cutaneous B-cell lymphomas

Lorenzo Cerroni *Helmut Kerl*

In the past, studies on malignant lymphoproliferative disorders of the skin were concerned mainly with lymphomas of the T-cell type. In recent years, through the synthesis of classical morphological studies and progress in immunology and molecular biology, it has been recognized that B-cell lymphomas that arise in the skin (primary cutaneous B-cell lymphomas or PCBCLs) represent a distinct and very important group of extranodal lymphomas.[1] They occur far more frequently than was generally believed. The widespread use of immunohistochemical and molecular genetic techniques has revealed that many of the cases classified in the past as cutaneous B-cell pseudolymphomas in fact represent low-grade malignant B-cell lymphomas of the skin.[2,3]

It is extremely important to emphasize that the treatment strategies for PCBCLs are completely different from those applied to other malignant lymphomas. It is therefore crucial to distinguish PCBCLs from secondary cutaneous manifestations of extracutaneous (usually nodal) B-cell lymphomas. PCBCL is defined as the presence of cutaneous disease alone with no evidence of extracutaneous spread over a period of at least 6 months after complete staging procedures.[4,5]

There are still many problems relating to the classification of PCBCLs. Some authors maintain that they represent, for the most part, B-cell lymphomas of germinal centre cell origin, whereas others believe that the majority consist of marginal zone, lymphomas of mucosa-associated lymphoid tissue-like (MALT-like) lymphomas.[6-9] There is also a view that all PCBCLs should be classified as skin-associated lymphoid tissue-type ('SALT-type B-cell lymphoma'), irrespective of morphological immunophenotypical and molecular patterns.[10] A classification of PCBCLs has been recently proposed by the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer (EORTC) (Table 1.1).[4]

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Table 1.1 EORTC classification of cutaneous lymphomas[4]

T-cell lymphomas	*B-cell lymphomas*
Indolent behaviour	*Indolent behaviour*
Mycosis fungoides	Follicle centre cell lymphoma
Mycosis fungoides with follicular mucinosis	Immunocytoma (marginal zone B-cell lymphoma)
Pagetoid reticulosis	
Large cell cutaneous T-cell lymphoma, CD30+	
Anaplastic	
Immunoblastic	
Pleomorphic	
Lymphomatoid papulosis	
Aggressive behaviour	*Intermediate behaviour*
Sézary syndrome	Large B-cell lymphoma of the leg
Large cell T-cell lymphomas, CD30-	
Immunoblastic	
Pleomorphic	
*Provisional entities**	*Provisional entities**
Granulomatous slack skin	Intravascular large B-cell lymphoma
CTCL, pleomorphic small/medium-sized	Plasmacytoma
Subcutaneous panniculitis-like T-cell lymphoma	

*This group includes cutaneous lymphomas with insufficient data to delineate clear-cut clinicopathological entities.
CTCL = Cutaneous T-cell Lymphoma

Table 1.2 Antibodies useful for the diagnosis of cutaneous lymphoproliferative diseases in routinely-fixed, paraffin-embedded tissue sections

Antibody	*CD*	*Source*	*Main specificity*
PS1	3	Novocastra	Pan-T lymphocytes
I290	4	Novocastra	T-helper lymphocytes
54/B4	5	Novocastra	T lymphocytes, B-CLL
C8/144b	8	Dako	T-suppressor lymphocytes
270	10	Novocastra	CALLA, germinal centre cells
C3D-1	15	Dako	Reed-Sternberg cells, myeloid cells
L26	20	Dako	B lymphocytes
1F8	21	Dako	Dendritic reticulum cells
BerH2	30	Dako	Activated lymphocytes, Reed-Sternberg cells
DF-T1	43	Dako	T lymphocytes, monocytes, myeloid cells
UCHL1	45RO	Dako	T lymphocytes, monocytes, myeloid cells
N-CAM16	56	Novocastra	NK cells
PGM1	68	Dako	Monocytes/macrophages, myeloid cells
mb-1	79a	Dako	B-lymphocytes, plasmacells
mic-2	99	Dako	Leucocytes, Ewing's sarcoma
Ig		Dako	Immunoglobulin heavy and light chains
S100		Dako	T-zone histiocytes
MIB1		Dianova	Proliferating cells
124		Dako	*bcl-2* protein
TdT		Dako	Precursor lymphocytes
TIA-1		Coulter	Cytotoxic lymphocytes
Granzyme-B		Monosan	Cytotoxic lymphocytes
ALK-1		Dako	t(2;5) fusion protein
CS1–4		Dako	EBV-latent membrane protein

All antibodies are to be used after antigen retrieval treatment (heat retrieval).
B-CLL = B-cell chronic lymphocytic leukaemia; CALLA = common acute lymphoblastic leukemia antigen; NK = natural killer; EBV = Esptein-Barr virus.

PCBCLs must be differentiated from benign (reactive) infiltrates of B-lymphocytes within the skin (B-cell pseudolymphomas). The differentiation of benign from malignant cutaneous B-cell infiltrates relies upon the evaluation of a constellation of clinical, histopathological, immunophenotypical and molecular criteria.[11] A list of the most useful antibodies for the analysis of cutaneous lymphoproliferative disorders is summarized in Table 1.2. The most important criteria for diagnosis are the clinicopathological correlation and detection of clonality using immunohistology and/or molecular genetics, which can be studied on routinely-fixed, paraffin-embedded biopsy specimens. Unfortunately, however, in approximately 30% of PCBCL cases neoplastic cells neither express immunoglobulin light chains nor show a monoclonal band with polymerase chain reaction (PCR) analysis of the J_H gene rearrangement.

A small percentage (about 20%) of PCBCLs harbour *Borrelia burgdorferi* DNA sequences within specific skin lesions.[12,13] The presence of *B. burgdorferi* underlines the analogy between B-cell lymphomas of the skin and those of the gastric mucosa, where, at least in some cases, infection by *Helicobacter pylori* is considered to be a causative agent.[14,15] This analogy may also imply that, at least in a small proportion of patients, antibiotic treatment could induce regression of skin lesions.

In the following, we will illustrate the most common types of PCBCL, as well as the most important among the extracutaneous B-cell lymphomas that can present with specific (secondary) skin manifestations.

CUTANEOUS FOLLICLE CENTRE LYMPHOMA

Cutaneous follicle centre lymphoma (FCL) is defined as the neoplastic proliferation of germinal centre cells confined to the skin.[16] It represents a common subtype of PCBCL.

Clinically patients present with solitary or grouped reddish papules, plaques or tumours which, especially on the trunk, can be surrounded by erythematous patches. Preferential locations are the scalp and forehead or the back. Ulceration is uncommon. Lesions located on the back have been named in the past 'reticulohistiocytoma of the dorsum' or 'Crosti's lymphoma'.[17] The prognosis for patients with cutaneous FCL is favourable. Recurrences are observed in about 50% of the cases, but dissemination to internal organs is rare.

HISTOPATHOLOGY

Cutaneous FCLs histologically show nodular or diffuse infiltrates within the entire dermis often extending into the subcutaneous fat.[18] The epidermis is spared as a rule. A clear-cut follicular pattern with the formation of neoplastic germinal centres is observed only rarely (Fig. 1.1). In these cases, the monoclonality of the germinal centres has been proven by immunohistology or by PCR analysis of the J_H gene rearrangement after microdissection of the germinal centre cells.[19] Morphologically centroblasts and centrocytes predominate within the neoplastic infiltrate, admixed with a variable number of immunoblasts, small lymphocytes and histiocytes and, in some cases, eosinophils and plasma cells. Some cases show the cytomorphological appearance of large cell lymphomas.[20]

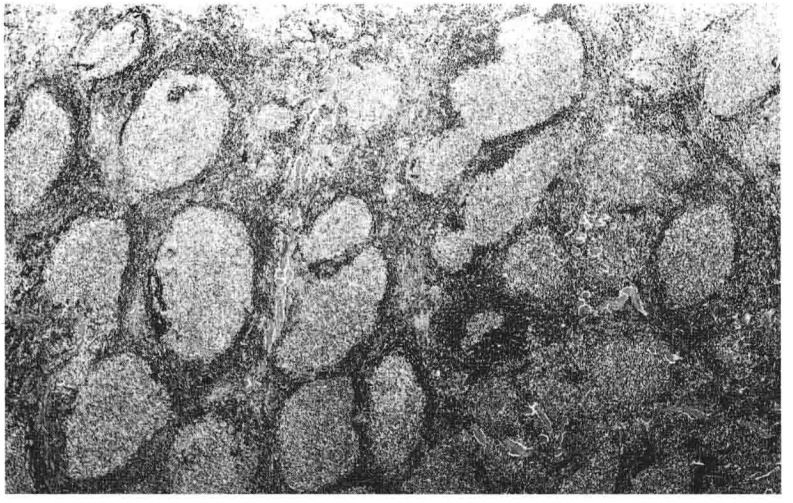

Fig. 1.1 Cutaneous follicle centre lymphoma, follicular. Irregular follicles with scant mantle zone.

An accompanying infiltrate of small T-lymphocytes and histiocytes/macrophages is usually present, and can predominate in some instances. Cases where a few B-cell blasts are admixed with numerous T-lymphocytes have been classified as 'T-cell rich B-cell lymphomas'.[21,22]

The tumour cells express monotypical surface immunoglobin (Ig) and B-cell-associated antigens (CD20, CD79a). They are CD5-, CD10- and CD43-negative. Staining for *bcl-2* protein (Bcl-2) yields negative results, which is a major difference from nodal FCL.[23] When neoplastic follicles are present they are characterized by an irregular network of CD21-positive follicular dendritic cells, and show CD10 positivity. In about 20% of skin FCLs an aberrant positivity for MT2 (CD45RA) can be observed in neoplastic germinal centres.[24] MT2-positivity is never found within reactive germinal centres, and can be considered to be a useful tool in differentiating cutaneous FCL from B-cell pseudolymphomas. Other useful immunohistochemical features for differential diagnosis are the lower degree of proliferative activity detected by the MIB-1 antibody in malignant germinal centres, as opposed to the strong MIB-1-positivity of reactive ones (Fig. 1.2), and the presence of CD10+ cells in interfollicular areas.

The interchromosomal 14;18 translocation, typically found in nodal follicular lymphomas, is not present in cutaneous FCLs.[23,25] Analysis of the J_H gene reveals monoclonal rearrangement in the majority of cases.

Synthesis of morphological, immunohistochemical and molecular data suggests that FCLs originating in the lymph nodes and the skin, although characterized by a similar morphological pattern, share different pathogenic mechanisms.

CUTANEOUS MARGINAL ZONE LYMPHOMA

Marginal zone lymphoma (MZL) has been recently recognized as a distinct variant of low-grade malignant PCBCL. It is closely related to immunocytoma and MALT-lymphomas.[3,26]

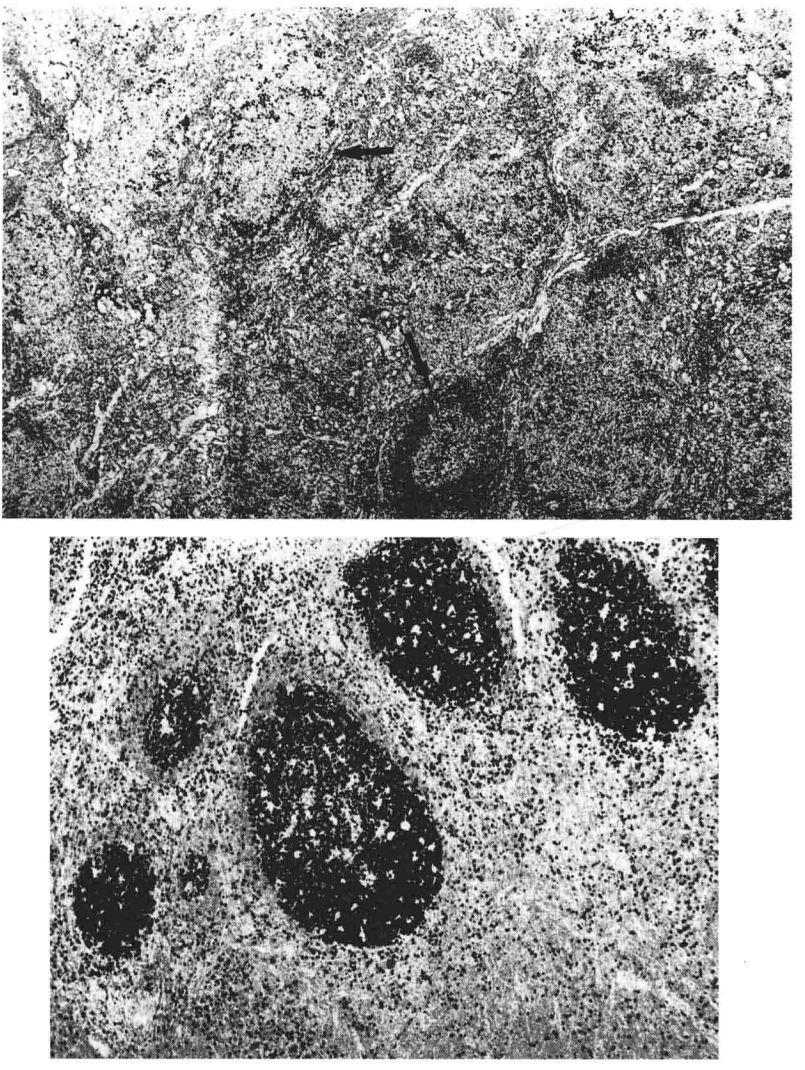

Fig. 1.2 **(A)** Cutaneous follicle centre lymphoma, follicular; note low proliferation rate within neoplastic follicles as detected by immunohistology (arrows) (antibody MIB-1). **(B)** By contrast, reactive germinal centres within a tonsil display a strong MIB-1 positivity.

Clinically patients present with recurrent red to reddish-brown papules, plaques and nodules localized preferentially on the upper extremities or the trunk. Generalized lesions can be observed in a minority of patients. The prognosis is excellent. In a recent study no patient showed internal involvement after a mean follow-up of more than 4 years.[3]

HISTOPATHOLOGY

Histology shows patchy, nodular or diffuse infiltrates involving the dermis and subcutaneous fat.[3] The epidermis is spared. A characteristic pattern can be observed at low power: nodular infiltrates, sometimes containing reactive germinal centres, are surrounded by a pale-staining population of small to medium-

sized cells with indented nuclei, inconspicuous nucleoli and abundant pale cytoplasm (variously described as marginal zone cells, centrocyte-like cells, or monocytoid B-cells) (Fig. 1.3). In addition, plasma cells (at the margins of the infiltrate), lymphoplasmacytoid cells, small lymphocytes and occasional large blasts are observed. Eosinophils are also a common finding. In some cases there may be a granulomatous reaction with epitheloid- and giant cells.

The centrocyte-like cells reveal positivity for CD20, CD79a and Bcl-2, and negativity for CD5 and CD10. In about 65% of cases, intracytoplasmic monotypical expression of immunoglobulin light chains can be observed. The monoclonal population of B lymphocytes is characteristically arranged at the periphery of cellular aggregates (Fig. 1.4). Staining with the monocytoid B-cell-related antibody Ki-M1p shows a positive reactivity of neoplastic cells with a characteristic intra-

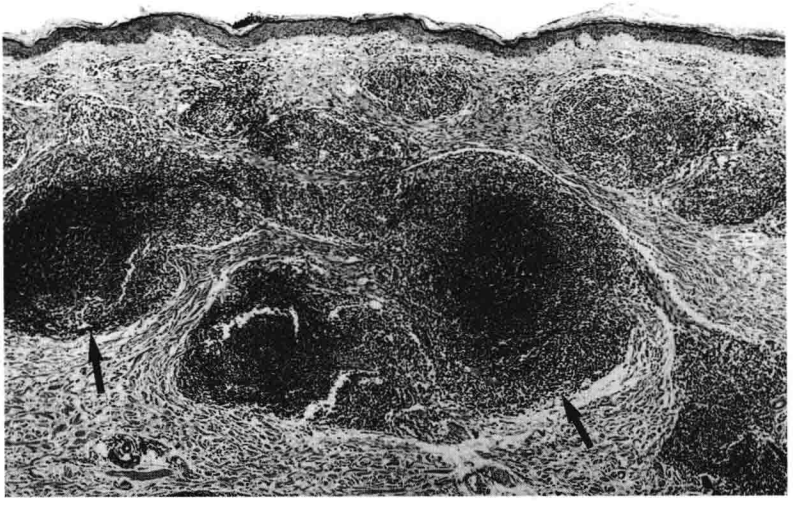

Fig. 1.3 Cutaneous marginal zone lymphoma. Typical architectural pattern of the lesion characterized by nodular infiltrates, sometimes containing reactive germinal centres, surrounded by a pale staining population of small to medium-sized cells with indented nuclei, inconspicuous nucleoli and abundant pale cytoplasm (arrows).

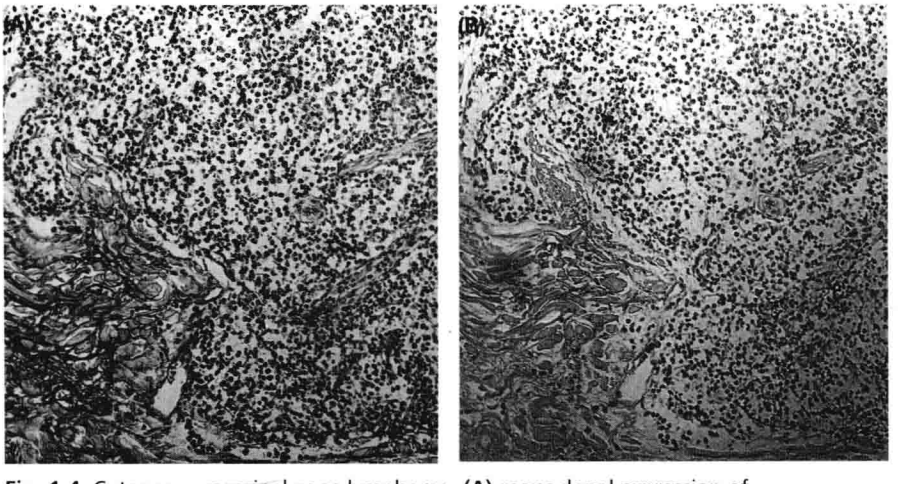

Fig. 1.4 Cutaneous marginal zone lymphoma. **(A)** monoclonal expression of immunoglobulin light chain kappa. **(B)** immunohistochemical reaction for immunoglobulin light chain lambda is negative.

cytoplasmic granular pattern. Monoclonal rearrangement of the J_H genes can be observed in the majority of cases.

CUTANEOUS IMMUNOCYTOMA

Cutaneous immunocytoma is defined as a proliferation of small lymphocytes, lymphoplasmacytoid cells and plasma cells with monotypical intracytoplasmic immunoglobulins. Primary cutaneous immunocytoma differs from nodal immunocytoma in that patients do not show features of Waldenström's macroglobulinæmia, and have an excellent prognosis and response to treatment.[27] Some authors consider immunocytoma and MZL of the skin to be a single entity of low-grade malignant cutaneous B-cell lymphoma.[10,28]

Clinically patients present with solitary, or grouped, erythematous to reddish-brown plaques or dome-shaped tumours that are found especially on the lower extremities. Generalized lesions are rare. Immunocytoma can arise in skin areas affected by acrodermatitis chronica atrophicans, and may be linked to infection by *B. burgdorferi*. In fact, *B. burgdorferi* DNA sequences have been demonstrated using PCR analysis in cutaneous lesions from three out of four patients tested.[12] The prognosis is excellent, although local recurrences can be observed.

HISTOPATHOLOGY

The architectural pattern is characterized by dense, monomorphous, nodular or diffuse infiltrates with involvement of the dermis and subcutis (Fig. 1.5).[3,29] The

Fig. 1.5 Cutaneous immunocytoma. Dense, homogeneous proliferation of small to medium-sized cells.

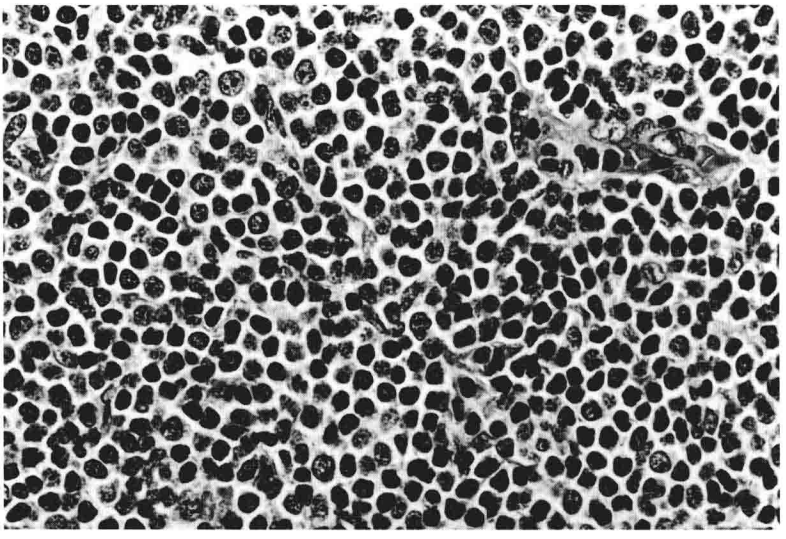

Fig. 1.6 Cutaneous immunocytoma. Lymphoplasmacytoid cells admixed with small lymphocytes and a few blasts.

epidermis is usually spared. The predominating cell types are lymphoplasmacytoid cells and small lymphocytes (Fig. 1.6). In addition, plasma cells are usually present, often located at the periphery of the infiltrates. Periodic acid Schiff-positive intranuclear inclusions (Dutcher bodies) are observed sometimes and represent a valuable diagnostic clue. Reactive germinal centres can be found in a few cases.

Neoplastic cells express monoclonal cytoplasmic immunoglobulins in most cases. In contrast to nodal immunocytoma, which is characterized by intracytoplasmic IgM, cutaneous lesions more often show IgG positivity. Cells are positive for CD20, CD79a and Bcl-2, and negative for CD5. An aberrant positivity for CD43 is found in about 50% of cases. Molecular analysis reveals monoclonal rearrangement of the J_H gene in most lesions.

CUTANEOUS PLASMACYTOMA

Cutaneous plasmacytoma is a B-cell lymphoma that is characterized by the clonal proliferation of plasma cells primarily affecting the skin, in the absence of bone marrow involvement (extramedullary plasmacytoma).[30,31] This type of cutaneous B-cell lymphoma is exceedingly rare.

Patients present clinically with solitary, clustered, or, in exceptional cases, generalized erythematous, reddish-brown or violaceous cutaneous/subcutaneous plaques or tumours. There is a predilection for the head and trunk. Cutaneous plasmacytoma occurs mostly in elderly male patients. The prognosis is controversial. In fact, although some reports have claimed that solitary lesions have a very good prognosis, comparable to that of solitary extramedullary plasmacytoma arising in other tissues, the development of multiple myeloma or systemic soft-tissue metastases have been observed in some patients.

HISTOPATHOLOGY

The tumour consists of dense nodules and/or sheets of cells within the entire dermis and subcutis (Fig. 1.7).[32] Mature and immature plasma cells with varying degrees of atypia predominate (Fig. 1.8). Dutcher bodies and Russell bodies are found occasionally. Small, reactive lymphocytes are few or absent. In a few cases

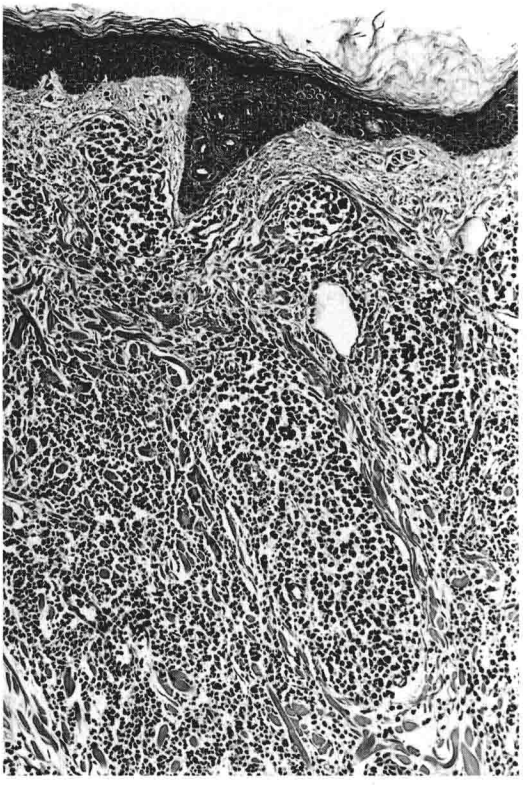

Fig. 1.7 Cutaneous plasmacytoma. Nodules of plasma cells within the dermis.

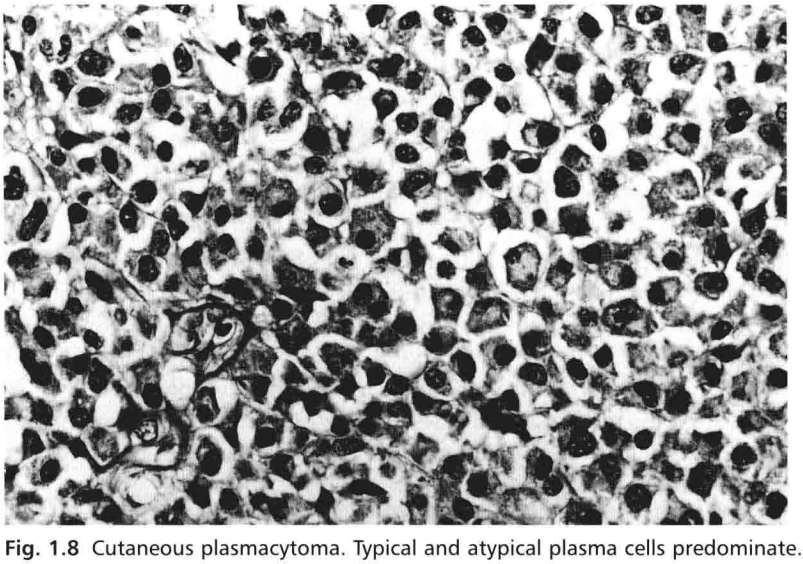

Fig. 1.8 Cutaneous plasmacytoma. Typical and atypical plasma cells predominate.