UPDATE ON LYMPHOMA PATHOLOGY: V SKIN LYMPHOMAS

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INTRODUCTION

We conclude this series of articles with a review of cutaneous lymphomas. Over 90% of these arise in the skin[1]. Skin can, however, be involved in the late stages of an internal lymphoma (usually of lymph node origin) when the prognosis will be much worse than for primary cutaneous lymphoma. Staging investigations are therefore required to support a diagnosis of primary cutaneous lymphoma.

Three quarters of all skin lymphomas are of T-cell type[1], a finding unique for all sites of lymphoma, nodal or extranodal. Normal skin contains very few lymphocytes. These are mostly T-cells which maintain contact with specialized antigen-presenting histiocytes in the epidermis (Langerhans cells). Cutaneous T-cells, however, proliferate considerably in the many different inflammatory diseases, e.g. eczema and psoriasis, to which skin is subject[2].

Skin lymphomas are also unusual in presenting obvious lesions to both patient and clinician throughout the course of the disease, which can span many years. Few skin lymphomas can be cured but most can be controlled by treatment. The clinical appearance can range from a single nodule to a red scaly rash covering most of the body.

Classification

Although long considered a problem area, classification of primary cutaneous lymphomas is at last becoming clear, easily applicable and clinically relevant, due principally to the following developments:

- application of the REAL classification (see Part I)
- discovery that CD30 antigen expression (see Information Box, Part III) is a powerful prognostic factor in large T-cell lymphomas
- recognition that B-cell cutaneous lymphomas are analogous to their internal counterparts
- recognition that small cell lymphomas of either T-cell or B-cell type can undergo large cell (high grade) transformation (just as for internal lymphomas).

CUTANEOUS T-CELL LYMPHOMAS

As in most other types of lymphoma, cutaneous T-cell lymphomas can be divided into major groups according to whether tumour cells are small or large (Figure 1). CD30 status is not helpful in the small cell tumours, but separates the large-cell tumours into low and high-grade categories. Mycosis fungoides dominates the group, accounting for 66% of all cutaneous T-cell lymphomas[1].

CYTOLOGY	CD30	NAME	FREQUENCY	GRADE
small cell	*	Mycosis fungoides	66%	low
large cell	+	CD30+ve large T-cell lymphoma	20%	low
large cell	–	CD30-ve large T-cell lymphoma	14%	high

Figure 1 Classification of primary cutaneous T-cell lymphoma
** result immaterial*

Mycosis Fungoides

Mycosis fungoides is a slowly-growing tumour of small T-lymphocytes which are localised to the skin and have a strong tendency to infiltrate the epidermis, thereby resembling the scanty lymphocytes normally present in skin (see above). Mycosis fungoides usually affects adults over the age of 30 years. Median age at diagnosis is 62 years[3].

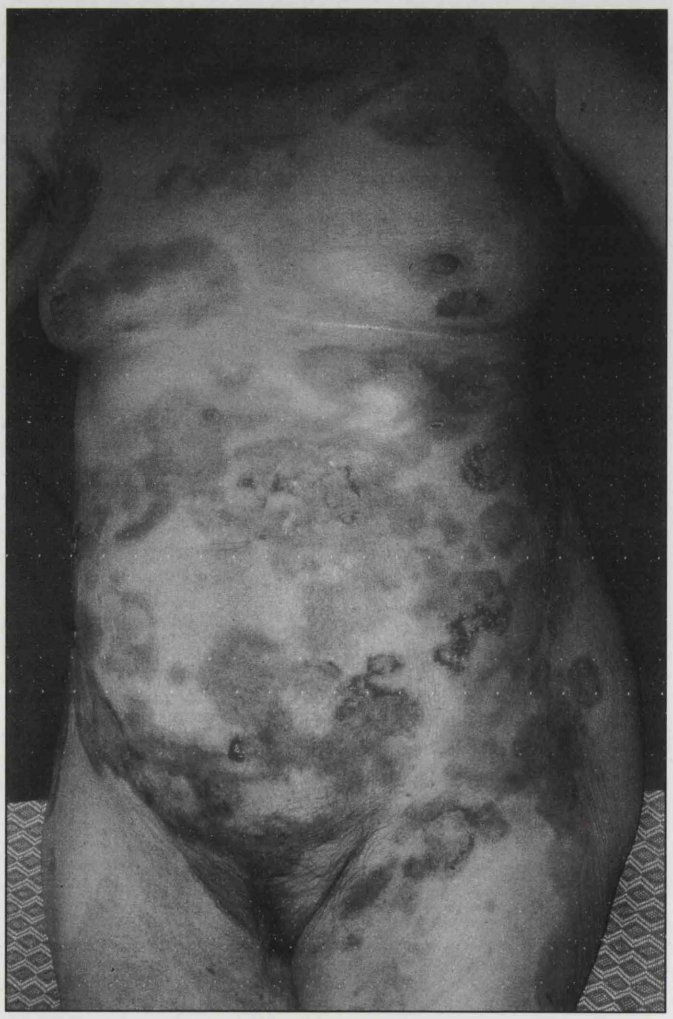

Figure 2 Mycosis fungoides. Extensive patches and plaques on trunk

The disease begins as red skin patches on the trunk or proximal limbs, frequently buttocks (Figure 2). The patches are slightly scaly, with an irregular outline, and often itchy. Lesions are initially flat, constituting the *patch stage* of the disease. Later on the lesions become thickened (*plaque stage*) and eventually ulcerated nodules can develop; this is the *tumour* stage which in its extreme form (and resemblance to fungi) prompted the original name of the disease. The three clinical stages of the disease are not strictly sequential as all types of lesion can coexist. Usually, however, the onset of the tumour stage is a late phase of the disease and signifies a poor prognosis.

The development of skin tumours is usually a consequence of high-grade transformation of the lymphoma, a phenomenon similar to that seen in low-grade B-cell lymphomas (see Part III). Histologically one sees a change from small cells to large cells. The large cells can be either CD30-positive or negative, a finding without prognostic significance in this context[6]. Rate of progression of mycosis fungoides is very variable, but a course of many years is usual. Median survival is reported as 9.7 years, with 5- and 10-year survival rates of 66% and 49% respectively[3].

Diagnosis in early stages of the disease can be difficult as the skin patches can simulate an inflammatory process such as eczema, psoriasis, or fungal infection. Biopsy usually shows a heavy band-like infiltrate of small lymphocytes at the base of the epidermis[2] (Figure 3). Lymphocytes extend into the epidermis (epidermotrophism) where they may be seen to possess highly folded or convoluted (cerebriform) nuclei. Biopsies repeated over time and careful correlation of the clinical and pathological findings will usually provide a diagnosis. In particularly difficult cases the diagnosis of lymphoma can now be established by the demonstration of T-cell monoclonality in biopsy material, using polymerase chain reaction[4].

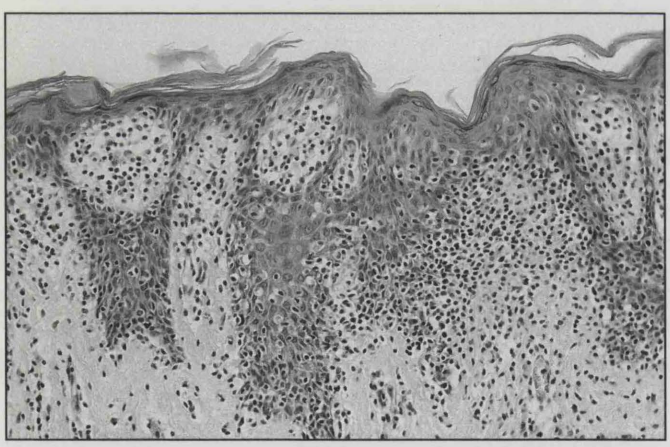

Figure 3 Mycosis fungoides. Numerous small lymphocytes infiltrate the skin

Sezary's syndrome is a very rare variant of mycosis fungoides in which the skin involvement quickly becomes generalised, giving rise to the clinical picture of *l'homme rouge*. Cerebriform lymphocytes appear in peripheral blood and prognosis is poor[2].

CD30-positive large T-cell lymphoma (anaplastic large cell lymphoma of skin)

A critical factor in the behaviour of large T-cell lymphomas has been found to be CD30 status, as determined in tissue section using an immunostain (see Part III, Information Box). CD30-positive tumours have a much better prognosis than negative ones[1,5]. CD30 status, however, is irrelevant in mycosis fungoides and B-cell tumours. The reason for the powerful prognostic value of CD30 in large T-cell lymphomas is unknown. Fortunately, the majority of cutaneous large T-cell lymphomas are CD30-positive[1].

Tumour cells in CD30-positive large T-cell lymphomas are often not only large but also pleomorphic, containing bizarre horseshoe-shaped or wreath-like nuclei, sometimes resembling Reed-Sternberg cells, an appearance identical to anaplastic large cell lymphoma. In fact the presence or absence of pleomorphism seems to make no difference to the clinical presentation and behaviour of this group of tumours[1]. Anaplastic large cell lymphoma of skin and CD30-positive large T-cell lymphoma can be regarded as identical.

CD30-positive large T-cell lymphoma can affect people at any age, not infrequently young adults[6]. The disease presents with reddish-brown skin nodules, either solitary or part of a widespread eruption. The lesions often ulcerate (Figure 4) and *frequently undergo spontaneous regression*, to be followed in due course by a crop of further nodules.

Despite the pleomorphic cytology (Figure 5) and sometimes disfiguring skin lesions, patients have an excellent prognosis with an estimated 5-year survival rate of 90%[7]. This is a far better outlook than for systemic anaplastic large cell lymphoma. Cutaneous anaplastic large cell lymphoma remains confined to skin and does not show the 2;5 translocation present in other types of anaplastic large cell lymphoma[5] (see Part III).

CD30-positive large T-cell lymphoma occurring as high-grade transformation of late stage mycosis fungoides has a poor prognosis[6].

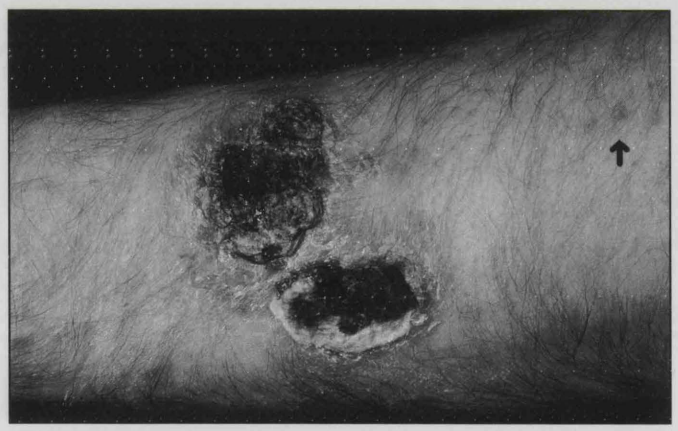

Figure 4 CD30-positive large cell lymphoma of skin (anaplastic large cell lymphoma). Two large crusted lesions are present on the arm and several early nodules (arrow). Lesions can spontaneously resolve.

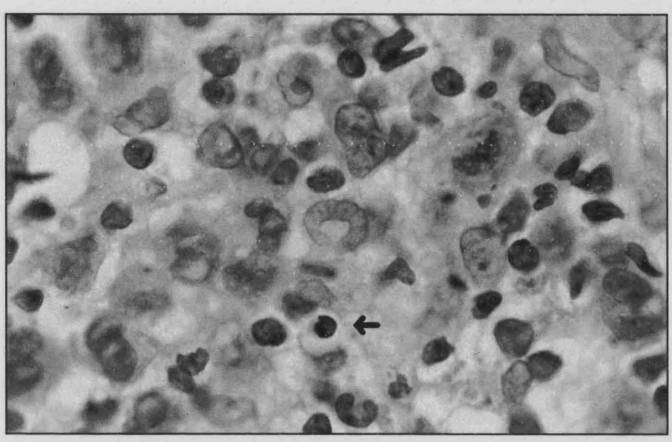

Figure 5 Bizarre tumour cells in anaplastic large cell lymphoma. Note horseshoe nucleus in centre. These cells are positive for CD30 on immunostaining. Normal lymphocyte nucleus for comparison (arrow).

Lymphomatoid papulosis is a manifestation of CD30-positive large T-cell lymphoma in younger individuals when the cycles of nodular eruption and healing are particularly marked[6].

CD30-negative large T-cell lymphoma
These tumours are rare and are the most malignant type of primary cutaneous lymphoma. Five-year survival rate is less than 20%[1]. The typical presentation is a solitary ulcerated nodule. CD30-negative large T-cell lymphomas can occur as high-grade transformation of mycosis fungoides; the prognosis of such transformed cases may not be so grave as tumours arising *de novo*[6].

CUTANEOUS B-CELL LYMPHOMAS

B-cell lymphomas are quite uncommon in the skin, amounting to only 25% of primary skin lymphomas. B-cell cutaneous lymphomas used to be regarded as a particularly confusing subject, but it is now becoming clear that they closely parallel B-cell lymphomas at other extra-nodal sites. Thus, true follicular lymphomas are very rare in skin, and their very existence is a matter of dispute[8]. A cutaneous follicular lymphoma showing the typical positive staining for BCL-2 (see Parts II and III) will almost certainly be metastatic, as will mantle cell lymphoma. Low grade B-cell lymphomas of skin are mostly of marginal zone type and outnumbered by high grade forms (just as in the stomach)[8] (Figure 6).

CYTOLOGY	NAME	FREQUENCY*	GRADE
small cell	marginal zone lymphoma	20%	low
large cell	diffuse large B-cell lymphoma	80%	intermediate

Figure 6 Classification of primary cutaneous B-cell lymphoma
**uncertain at present*

Marginal zone lymphoma of skin[11]
Marginal zone lymphoma presents as a red smooth surfaced nodule or cluster of nodules on any part of the body surface in adults[6,8] (Figure 7). Lesions persist indefinitely and slowly expand. On histology there is a dense infiltrate of small neoplastic lymphocytes usually admixed with some residual reactive lymphoid follicles (as in the stomach). The lesion can be difficult to distinguish from the lymphoid hyperplasia which may follow insect bites, but time and repeat biopsy will usually resolve the problem. The prognosis is excellent. Marginal zone lymphoma has the best prognosis of all cutaneous lymphomas.

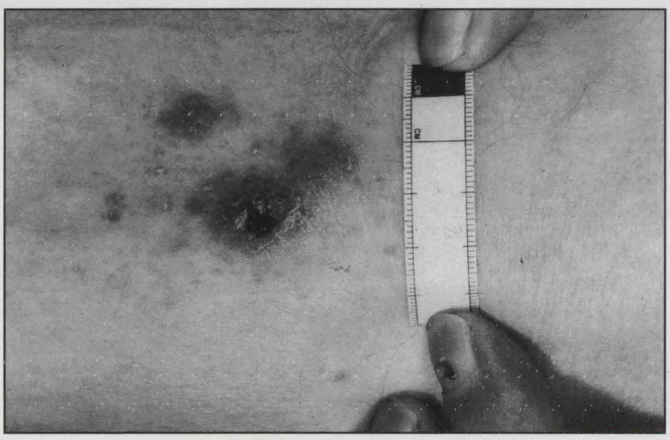

Figure 7 Marginal zone lymphoma on leg.

Evidence is accumulating that *Borrelia burgdorferi* infection can be a precursor of cutaneous marginal zone lymphoma, in much the same way that *Helicobacter pylori* predisposes the stomach to lymphoma (see Parts III and IV). *Borrelia burgdorferi* is a chronic bacterial infection (Lyme disease) transmitted by tick bites. DNA studies using the polymerase chain reaction have recently revealed evidence of *Borrelia burgdorferi* infection in 30% of cases of cutaneous marginal zone lymphoma in Scotland[9].

Since marginal zone lymphocytes are post-germinal centre (see Part III), a varying degree of plasmacytoid differentiation may be seen within the tumours. Tumours showing prominent plasmacytoid differentiation are sometimes referred to as immunocytomas and in rare extreme cases as cutaneous plasmacytomas"[6]. These tumours, however, appear to be variants of marginal zone lymphoma, not myeloma[10].

Large B-cell lymphomas of skin
There is uncertainty regarding the definition and prognosis of this group of tumours, some European authors including them in the disputed category of primary cutaneous follicle centre cell lymphomas[7]. In fact many large B-cell lymphomas of skin probably arise from high-grade transformation of marginal zone lymphomas.

Large B-cell lymphomas of skin often present as nodules on the head or trunk. Despite the high-grade histology, the prognosis is good and the tumours remain confined to skin. Five-year survival rate is estimated at 90%.

A subgroup of large B-cell lymphomas, however, occurring on the leg of elderly females, is believed to have a worse prognosis. At this site, tumours are more prone to relapse and eventual systemic spread. Five-year survival rate is about 60%[6].

SUMMARY OF CLASSIFICATION OF PRIMARY CUTANEOUS LYMPHOMAS

As we have seen, cutaneous lymphomas can be classified effectively using four simple variables:

- T or B cell
- small or large cell
- CD30 + or –
- *de novo* tumour or transformed (from low-grade)

When collated, these variables yield a total of eight primary cutaneous lymphomas (Figure 8).

CELL TYPE	NAME			PROGNOSIS
T-cell	Mycosis fungoides			good
	large cell	CD30+	*de novo*	good
			transformed	poor
		CD30–	*de novo*	very poor
			transformed	poor
B-cell	Marginal zone lymphoma			excellent
	Diffuse large B-cell lymphoma		*de novo*	moderate
			transformed	moderate

Figure 8 Cutaneous lymphomas in a nutshell

CONCLUSIONS

Cutaneous lymphomas, just like the wider family of lymphoma, cover a remarkable range of clinical appearance and malignant potential. In this series of five articles on lymphoma pathology we have reviewed all the main lymphoma types. Of these the most indolent of them all is probably marginal zone lymphoma of the skin; amongst the most malignant are diffuse large B-cell lymphoma and intestinal T-cell lymphoma.

The development of immunostains has transformed our ability to classify lymphomas. Diagnostic entities can be defined and identified with increasing precision. As a result, the number of categories of lymphomas now considerably exceeds the number of available treatments, but we can expect rapid development of treatment specificity and effectiveness. None of this would be possible without the firm foundation of lymphoma pathology.

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