**Introduction**

Primary cutaneous lymphoma is defined as lymphoma presenting in the skin with no extracutaneous dissemination at the time of diagnosis or for six months thereafter.

After the gastrointestinal tract, the skin is the second most common site of primary extranodal lymphoma. The clinical behaviour of cutaneous lymphomas is distinct from histologically similar lymphomas of lymph nodes and other sites.

The classification of primary cutaneous lymphomas is derived from two main groups, the European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organisation (WHO).

**WHO-EORTC classification primary cutaneous lymphomas**

**Cutaneous T-cell and NK-cell lymphomas**

- Mycosis fungoides (and variants and subtypes)
- Sézary syndrome
- Adult T-cell leukaemia/lymphoma
- Primary cutaneous CD30-positive lymphoproliferative disorders
- Subcutaneous panniculitis-like T-cell lymphoma
- Extracodal NK/T-cell lymphoma, nasal type
- Primary cutaneous peripheral T-cell lymphoma, unspecified

**Cutaneous B-cell lymphomas**

- Extracodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)
- Primary cutaneous follicle centre lymphoma
- Primary cutaneous diffuse large B-cell lymphoma, leg type and other

**Precursor haematologic neoplasm**

- Blastic plasmacytoid dendritic cell neoplasm (CD4+/CD56+ haematodermic neoplasm)

**Cutaneous T-cell and NK-cell lymphomas**

Cutaneous T-cell lymphomas represent a heterogeneous group of neoplasms which show considerable variation in clinical presentation, histopathology and prognosis.

**Mycosis fungoides**

Mycosis fungoides (MF) is a clinically and pathologically distinct form of cutaneous lymphoma characterised by an epidermotrophic infiltrate of small to medium sized lymphocytes. In the WHO-EORTC classification, the term is reserved for those cases having classical features in which there is progression from patches to plaques to tumours. MF represents almost 50% of all cutaneous lymphomas.

MF usually arises in late adulthood with a male predominance. The lesions tend to develop on the lower part of the trunk and thighs. MF typically has an indolent course with slow progression over years or decades.

The patch stage consists of ill defined patches of varying hue, often with a fine scale, that are irregular in size and shape with a random distribution. The plaque stage is characterised by well demarcated lesions which are often annular or arciform in arrangement. They are red to violaceous in appearance and occasionally scaly. Tumours usually develop in pre-existing lesions. The tumours are violaceous to deep red in colour with a tense shiny surface and ulceration may occur. The lesions are usually 1cm in diameter or more.

There is considerable literature on the histological diagnosis of mycosis fungoides, particularly in the early stages. Multiple biopsies over a period of time are often needed for a diagnosis. In the patch stage of MF a combination of architectural and cytological features is used to make the diagnosis.
These include epidermal lymphocytes and epidermotropism, intraepidermal lymphocytes with convoluted nuclei, Pautrier's microabscesses, lymphocytes with a clear perinuclear halo and lymphocytes aligned along the basal layer of the epidermis. There is overlap between MF and a number of inflammatory dermatoses, including most commonly pigmented purpuric dermatoses and follicular mucinosis. The patch and plaques stage are part of a progression. In the tumour stage, the infiltrate has a more monomorphic appearance and is dominated by atypical cells. The tumour cells in MF are CD3+, CD4+, CD8- and CD30-. In most cases the neoplastic lymphocytes of MF express the alpha beta TCR. The significance of demonstrable clonal TCR gene rearrangements in suspect lesions remains controversial.

**Myeloid lymphomas**

There are also variants and subtypes of MF which include folliculotropic MF, Pagetoid reticulosis and granulomatous slack skin. Sézary syndrome is regarded as a separate entity in the WHO-EORTC classification, but many regard it as a manifestation of MF, or the leukaemic stage of MF. It is defined by erythroderma, generalised lymphadenopathy and Sézary cells in the skin, lymph nodes and peripheral blood.

**Adult T-cell leukaemia/lymphoma**

Adult T-cell leukaemia/lymphoma (ATLL) is a T-cell lymphoma resulting from infection with human T-cell lymphotrophic virus type 1 (HTLV-1), a type C retrovirus. The virus is endemic in south western Japan and the Caribbean and is transmitted by sexual contact, breastfeeding and infected blood products. Skin manifestations are often the initial manifestation of ATLL and are found in all forms of the disease.

The lesions are often widespread and have many forms including erythematous patches, plaques, papules and tumours. Solitary lesions are unusual. There is some overlap in the histological appearance with that of mycosis fungoides.

**Primary cutaneous CD30+ lymphoproliferative disorders**

The primary cutaneous lymphoproliferative disorders are linked by the common histological features of large atypical lymphoid cells expressing CD30.

The primary cutaneous CD30+ lymphoproliferative disorders include: primary cutaneous anaplastic large cell lymphoma (C-ALCL), lymphomatoid papulosis, and borderline cases that do not fit clearly into these categories. Distinction between C-ALCL and lymphomatoid papulosis is not always possible on the basis of histological criteria, and classification is based on the clinical presentation and course as well as the histological appearance of the lesions. In borderline cases, clinical follow up may allow assignment to the appropriate group.

**Lymphomatoid papulosis**

Lymphomatoid papulosis is a chronic lymphoproliferative disorder characterised by the appearance of crops of papules, nodules and sometimes large plaques at different stages of development. Lesions spontaneously regress after several weeks or months. The lesions occur mainly on the trunk and proximal parts of limbs. There is a predilection for females in the third and fourth decades, but may also occur in children.

The histological appearance of lymphomatoid papulosis suggests it is a lymphomatous process and most would now regard this condition as a low grade cutaneous T-cell lymphoma, part of the spectrum of C-ALCL. Some still classify it as a pseudolymphoma. Because the histopathological and immunophenotypic features of lymphomatoid papulosis overlap with C-ALCL, the clinical appearance and course are important features in separating the two conditions and choosing treatment options. Lesions of C-ALCL tend to be few and localised whereas lymphomatoid papulosis presents as recurring crops of multiple, widely dispersed lesions which involute spontaneously.

There are three overlapping histopathological subtypes of lymphomatoid papulosis: types A, B and C.

**Lymphomatoid papulosis type A** is characterised by a wedge-shaped, mixed cellular dermal infiltrate which includes variable numbers of CD30+ large atypical cells similar to those seen on C-ALCL. The atypical cells may be multinucleated or resemble Reed-Sternberg cells. There is a background population of small lymphocytes, eosinophils, neutrophils and histiocytes. Epidermotropism is variable.

**Lymphomatoid papulosis type B** is an uncommon pattern seen in 10% of cases characterised by a pascular or band-like dermal infiltrate with epidermotropism. The predominant cell types are small to medium sized lymphocytes with cerebriform nuclei resembling mycosis fungoides. Large CD30+ cells are uncommon in this subtype.

**Lymphomatoid papulosis type C** lesions resemble C-ALCL and have a monotonous population of CD30+ large atypical cells with relatively few admixed inflammatory cells. The large atypical cells in lymphomatoid papulosis types A and C are CD30+, CD4+ and CD3+ similar to the cells in C-ALCL. The cells are negative for ALK-1. The immunohistochemistry marker MUM-1 is expressed in the large cells in types A and C, whereas the large cells in C-ALCL are usually MUM-1 negative. Clonal rearrangement of alpha beta T-cell receptor genes has been identified in approximately 80% of lesions. No specific genetic abnormalities have been identified in lymphomatoid papulosis and the t(2;5) translocation seen in C-ALCL is not present.
The presence of a positive reaction for ALK-1 generally indicates cutaneous spread of primary systemic anaplastic large cell lymphoma rather than C-ALCL. The majority of the cases are of T-cell type and exhibit clonal beta or gamma TCR gene rearrangements.

**Subcutaneous panniculitis-like T-cell lymphoma**
The current WHO-EORTC classification confines this condition to those T-cell lymphomas which have a panniculitis-like histology and have an alpha beta T-cell phenotype. The alpha beta phenotype distinguishes it from cutaneous gamma/delta T-cell lymphoma, now sub-classified separately.

It is composed of cytotoxic CD8+ T-cells producing subcutaneous nodules on the trunk and extremities. Haemophagocytic syndrome may occur in 15% of cases. The classical histological appearance is of atypical cytotoxic T-cells rimming adipocytes in the subcutis.

**Extranodal NK/T-cell lymphoma, nasal type**
Extranodal NK/T-cell lymphoma nasal type is the best characterised of the NK/T-cell lymphomas. It is almost always associated with Epstein Barr virus. This form of lymphoma is common in Asia, South and Central America and Mexico but uncommon elsewhere. It presents most commonly in the nasal region, often with midline facial destructive disease (‘lethal midline granuloma’). This is an aggressive lymphoma with a short median survival and high mortality rate.

**Primary cutaneous peripheral T-cell lymphoma, unspecified**
This is a heterogeneous group of T-cell lymphomas which do not fit well into one of the well defined subtypes of T-cell lymphoma. These lymphomas originate from mature transformed T-cells. They account for less than 10% of cutaneous T-cell lymphomas. This group includes Primary cutaneous aggressive epidermotrophic CD8+ T-cell lymphoma, cutaneous gamma/delta positive T-cell lymphoma and primary cutaneous CD4+ small/medium sized pleomorphic T-cell lymphoma.
Mature B-cell neoplasms
- Cutaneous marginal zone B-cell lymphoma (MALT-type)
- Primary cutaneous follicle centre lymphoma

Growth patterns
- Follicular
- Follicular and diffuse
- Diffuse
- Cutaneous diffuse large B-cell lymphoma, leg type
- Cutaneous diffuse large B-cell lymphoma, others

Cutaneous marginal zone B-cell lymphoma (MALT-type)
The majority of low grade B-cell lymphomas appear to be of this type. It occurs most commonly in adults with a male predominance. Lesions occur predominantly on the arms and trunk. They are frequently multifocal in contrast to primary cutaneous follicular centre lymphoma. Extranodal marginal zone lymphomas affect the GI tract, salivary gland, ocular, lung, thyroid, breast and skin in approximately 11% of cases. The histological features include an infiltrate affecting the mid dermis and subcutis composed of marginal zone cells containing small cleaved nuclei and variably abundant amphophilic cytoplasm. The neoplastic cells surround reactive germinal centres. The cells are CD20+, CD5-, CD10- , CD23- and demonstrate light chain restriction. There is usually an indolent course.

Primary cutaneous follicle centre lymphoma
It is only recently that this low grade primary cutaneous lymphoma has been established as an entity that is distinct from conventional nodal follicular lymphoma and primary cutaneous marginal zone lymphoma. It accounts for 60% of cutaneous B-cell lymphomas. It is a disease of adults, rarely occurring in children. Most cases affect the scalp, forehead and trunk and are usually single, erythematous plaques or tumours. The prognosis is excellent with a five-year survival of 95%. The neoplastic cells demonstrate light chain restriction of neoplastic follicle centre cells. The cells are Bcl-6- and CD10+. Cutaneous follicular centre lymphoma will include lesions that are either follicular or diffuse composed of a mixture of centrocytes and centroblasts. Some of these tumours would have been called diffuse large B-cell lymphoma in the previous WHO classification.

Cutaneous diffuse large B-cell lymphoma, leg type
This subtype accounts for 20% of cutaneous B-cell lymphomas. 10 – 15% of cases do not present on the leg. They may be systemic dissemination and there is a 55%, five-year survival rate. The features are of a diffuse dermal infiltrate of large atypical B-cells which are CD20+ and Bcl-2+. Bcl-6 may be positive or negative.

Cutaneous diffuse large B-cell lymphoma, others
The best defined lymphoma in this group is intravascular large B-cell lymphoma, which is a rare lymphoma and consistent of large neoplastic B-cells confined to the vascular lumina. The skin and CNS are the most common sites of involvement. Other lymphomas in this group include T-cell rich/histiocyte rich B-cell lymphoma and anaplastic or plasmablastic lymphoma.

References

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Dr Fahey completed her Bachelor of Medicine and Bachelor of Surgery in 1998 at Monash University Medical School. During her time at Monash, she also completed a Bachelor of Medical Science – Forensic Pathology. She is a Fellow of the Royal Australasian College of Pathologists and has held appointments at a number of hospitals. Dr Fahey was a Registrar in Anatomical Pathology at the Royal Women’s and Royal Children’s Hospitals in 2004 and at the Royal Melbourne Hospital for four years from 2000 – 2003 and again in 2005. She worked as a Consultant Pathologist at the Royal Melbourne and Western Hospitals between 2005 – 2007 before commencing at Melbourne Pathology. Her special interests include dermatopathology, gastrointestinal pathology and breast pathology.