原文題目(出處)：	Update on extranodal lymphomas. Conclusions of the Workshop held by the EAHP and the SH in Thessaloniki, Creece (Histology 2006. 48, 481-504)
原文作者姓名：	E campo, A Chott, M C Kinney, L Leoncini, C J L M Meijer, C S Papadimitriou, M A Piris, H Stein & S H Swerdlow
通訊作者學校：	Aristotelian University of Thessaloniki
報告者姓名(組別)：	陳靜怡
報告日期：	2007.12.31

內文：

Abstract

Extranodal lymphoma 的分級與治療受制於 lymphoma 種類的多樣性與其中許多種類的稀少性，因此 European Haematopathology Association 與 the Society for Hematopathology 共同舉行一個研討會，共回顧討論 99 個病例，焦點在於矛盾最多的 cutaneous B-cell lymphoma、other extranodal B-cell lymphoma、plasmablastic lymphoma 與 anaplastic large-cell lymphoma in extranodal sites。

Introduction

Extranodal lymphoma 的診斷、分級與適當治療在 routine lymphoma diagnosis 為經常的挑戰，因為 extracnodal lymphoma 具有 variety of morphologies、molecular alterations and clinical presentations。在 extranodal site 發現的 B-cell 或 T-cell lymphoma 意謂對病人有不同 risks 且需要不同的治療方針。

EAHP 與 SH 在 2004 舉辦研討會回顧了 99 病例並在這篇 report 中發表結論。

Highlights of cutaneous lymphomas

Primary B-cell lymphoma 這個 group 可分為下列四種:

1. primary cutaneous marginal zone B-cell lymphoma
2. primary cutaneous follicle centre lymphoma (PCFCL)
3. primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL，leg type)
4. primary cutaneous large B-cell lymphoma，orther

新的資料顯示 2、3、4 項確實為不同的 clinicopathological entities，擁有個別的 immunophenotypical 與 genotypic 特色。

Primary cutaneous follicle centre lymphoma

1. a tumor of neoplastic follicle centre cells
   (1) centrocytes： small and large cleaved follicle centre cells
   (2) centroblasts： large non-cleaved follicle centre cells with prominent nuclei

2. 位置：head and trunk
3. growth pattern: follicular、follicular and diffuse、diffuse
4. Prognosis: excellent，5-year survival rate—95%
5. Immunophenotype：B cell(CD20+，CD79a+)，Bcl-6(+), Bcl-2(-) or weak +，Mum-1/IRF4-，CD10-/+ diffuse lesion 大部份 negative。
6. (1) t(14, 18)常在 systemic follicular lymphomas 中見到，部份 systemic diffuse large B-cell lymphoma 無此現象。
   (2) inactivation of p15 and p16 tumor suppressor genens by promotor hypermethylation

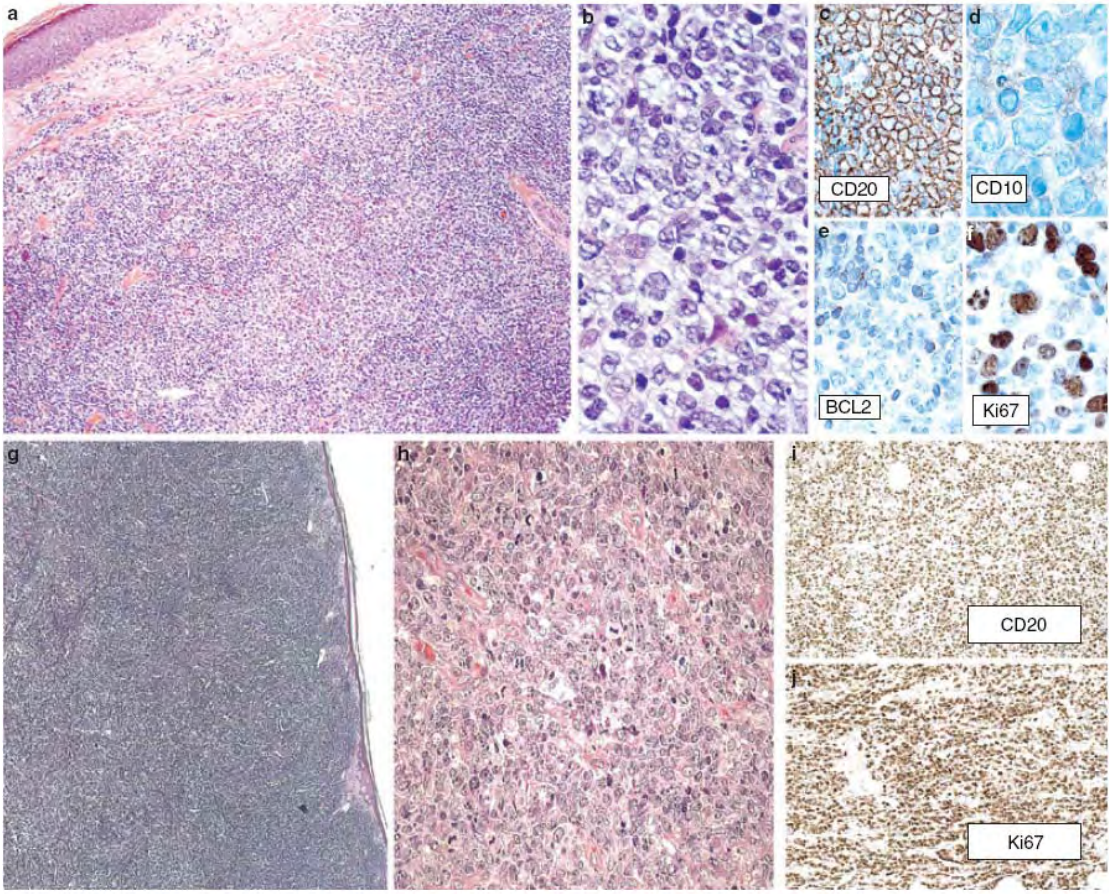


Figure 1. a–f, Primary cutaneous follicle centre lymphoma. a, Nodular pattern. b, Centroblastic predominance. c, CD20. d, CD10. e, Bcl-2. f, Ki67. g–j, Primary cutaneous diffuse large B-cell lymphoma, leg type. g,h, morphology, H&E. i, CD20. j, Ki67. Cases contributed by C. Girardet (A6) and R. S. Robertorve (A8).

名詞解釋

MUM-1 – transcrption factor, regulate by Bcl-6, 使 B-cell→ plasma cell

IRF4 – interferon regulatory factor, 使 B-cell → plasma cell

Bcl-6 – B cell lymphoma 6 protein, repressor factor, 表現在 germinal center B cells 與 activated B-cells

Bcl-2 – anti-apoptotic gene，與 myc 一起作用 -> lymphoma

Myc – cell cycle mitogen promoting gene，oncogene

P15，P16 – tumor suppressor gene，hypermethelation → inactivation
FOX-P1 – forkhead box protein P1，transcription factor

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL，leg type)

1. mixture of neoplastic centroblasts and imunoblasts (round cells)
2. 位置：lower leg
3. Prognosis: 5-year survival rate—55% in the Dutch and Austrian cases
   (1) 長在腳上比長在其它位置預後更差。
   (2) single lesion on one leg：disease-related 5 year survival rate – 100%
   (3) multiple lesion on one or both legs：disease-related 5 year survival rate –45%(one)，36%(both)
4. Age and Gender：elderly female
5. Immunophenotype：B-cell(CD20+，CD79a+)，MUM-1/IRF4+，FOX-P1+，Bcl-6+，Bcl-2+，CD10-
6. (1) t(14, 18) absent
   (2) recent studies：translocations involving myc，Bcl-6 and IgH genes indicating activated B cell gene expression profile
   (3) inactivation of p15 and p16 tumor suppressor genens by promotor hypermethylation

Primary cutaneous large B-cell lymphoma，other

1. morphological variants
   (1) anaplastic or plasmablasitc subtypes
   (2) T-cell/histiocyte-rich large B–cell lymphomas：large scattered B cells in a background of numerous reactive T cells.
   (3) Primary cutaneous intravascular large B-cell lymphoma, may be included Generally a skin manifestation of a systemic lymphoma，primary cases -> rare
2. clinically similar to PCFCL and PCMZL
3. 位置：head、trunk、extremities
4. Prognosis：excellent

Primary cutaneous T-cell lymphoma(primary CTCL)

1.Tyes
   (1) Mycosis fungoides – skin rash, mushroom necrosis
   (2) Sezary syndrome – advanced mycosis fungoides, 5%
   (3) Primary cutaneous CD30+ lymphoproliferative diseases

(4) Others – 10%, clinically aggressive(few exceptions)
Cases with a favorable prognogis -- Small/medium-sized pleomorphic CTCL with a CD4+ phenotype (provisional entity)

2. Changes
(1) subcutaneous panniculitic-like T-cell lymphma
1. α/β T-cell phenotype -- indolent
2. γ/δ T-cell phenotype – aggressive
兩者應分開為不同的 entities
(2) 下列三類 disorder 原本被包含在現行 WHO classification post-transplant lymphoproliferative disorder (PTLD)中，被提出應成為 provisional entities
1. aggressive epidermotropic CD8+ CTCL
2. cutaneous γ/δ T-cell lymphoma (including SPLCTCL with a γ/δ phenotype)
3. primary cutaneous small-medium CD4+ T cell lymphoma
PTCL 則保留給原先其它無法歸屬於這三類疾病的 PTCL。

Plasmacytoid dendritic cell tumors
1. Cell origin – monotonous proliferation of cells with lymphoblast-like morphology and expression of CD4 and CD56 phenotype
因為 CD56(+)，所以最初認為與 NK cell 有關，在 WHO 分類中被歸類為 blastic NK-cell lymphomas
2. 新的 antibodies 發現這類細胞非 NK cell，經歷多次重新命名最後稱為 plasmacytoid dentritic cells
lymphoblast -> T-associated plasma cell -> plasmacytoid T cell -> plasmacytoid monocytes -> plasmacytoid dentritic cells
3. Immunophenotype—Table 2.
4. Functions – the functional profile of dendritc cells
(1) Secretion of IFN-α,β
(2) Express TLR-7 and TLR-9
(3) Promote function of NK, B, and T cells
可直接調節 T-cell，聯結 innate 與 adaptive immune responses，因此 plasmacytoid dendritic cell 具有部份"evolutionary immunological memory, 讓器官可受到 first-line、immediately effective defense system 的保護。

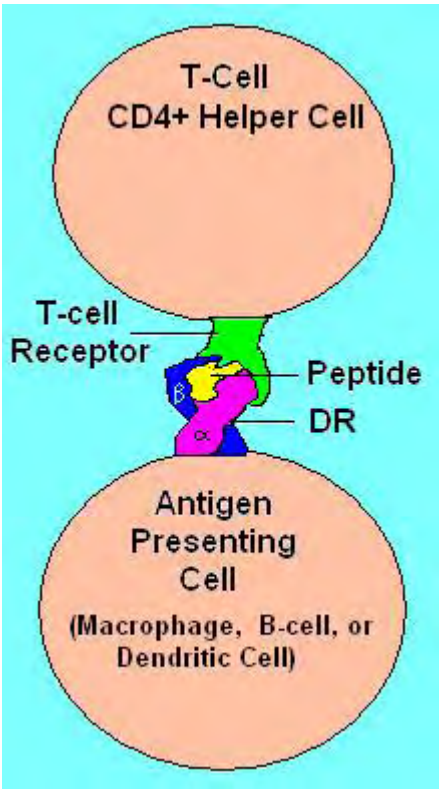
名詞解釋
TLR – Toll-like receptor family, 位於 dendritic cell 表面
功能 1. 辨認 pathogen
2. 活化 innate immune system

TLR-7, TLR-9 – IFN-α, β, λ induction

5. Immunophenotype

Table 2. Comparison of the immunophenotype of normal and tumoral plasmacytoid dendritic cells (PDC)

Marker	PDC in reactive lymph nodes	PDC tumours $N = 7$	
CD4	+	+	T-cell
CD56	−/(+)	+	NK-cell
HLA-DR	+	+	T-cell receptor
CD43	+	+	T-cell receptor
TCL1	−/(+)	+	T-cell lymphoma gene
CD123	+	+	Interleukin 3 receptor -- Tcell
CD45RA	+	+	Leukocyte common antigen, isoforms – naïve T cell
CD68	+	+/−	Histiocyte/Macrophage
Granzyme B	−	+/−	T_c-cell/NK cells
TdT	−	+/−	DNA polymerase, pre-B, pre-T cells
Perforin	−	−	
CD45RO	−	−	
Myeloperoxidase	−	−	
CD34	−	−	
CD20, CD3	−	−	



6. Histopathological feature
   (1) Immature lymphoblast-like cytology
   (2) Agranular cytoplasm
   (3) Cytoplasm full of microvesicles
   (4) Infiltration of the dermis
   (5) But consistent sparing the epidermis
   (6) Involvement of lymph nodes in the para/interfollicular areas
7. Clinical features
   (1) Age: elders
   (2) Manifest in the skin and bone marrow
   (3) Frequently evolve to an overt leukemia associated with an aggressive course
   (4) Death within 3 years despite initial response to therapy.

8. Plasmacytoid dendritic cell tumors 應與其它血液惡性腫瘤分開，

Thyroid lymphoma
Review
1. Prevalence: rare
   (1) 佔所有 thyroid neoplasms – 5%
   (2) 佔所有 lymphoma – 不超過 2.5%
   (3) 佔所有 extranodal lymphoma – 7%

2. Type of primary thyroid lymphoma
   (1) 50-80% -- diffuse large B-cell lymphoma (DLBCL)
   (2) 20-30% -- marginal zone B-cell lymphoma of mucosa associated lymphoid tissue type (MALT lymphoma)
   (3) no more than 12% -- follicular lymphoma
   (4) rare cases – plasmacytoma、Burkitt lymphoma、small lymphocytic lymphoma、anaplastic large cell lymphoma and peripheral T-cell lymphoma。
3. Clinical features
   (1) 大部份的 thyroid lymphoma 與 lymphocytic / Hashimoto's thyroditis 有關
   (2) Gender：female
   (3) Mean age：60
   (4) Stage:IE and IIE →90%
4. 5 year survival rate -- MALT type：60-100 %； DLBCL type：40-70%
   Prognostic indicators: (1) advanced age (2) advanced stage
   (3) type of neoplasm(MALT lymphoma or DLBCL)

The Workshop – 5 cases，none of MALT lymphoma

3 issues

1. Definition of primary thyroid lymphoma
   (1) a dominant thyroid lesion
   (2) primary complaint related to the thyroid
   (3) thyroid involvement at diagnosis
   (4) a history of Hashimoto's thyroiditis

   發生於 thyroid 的 secondary lymphoma，MALT lymphoma 與 DLBCL 所佔的比例較小，其它 lymphoma 所佔比例較大，發生在 thyroid 的 primary lymphoma 以 DLBCL 與 MALT lymphoma 居多，但仍要了解雖然 rare，uncommon lymphoma 也會發生在 thyroid，如同本篇提出的 5 個 cases (peripheral T-cell lymphoma，mantle cell lymphoma)，而且就像其它的 primary thyroid lymphoma，這 5 個 cases 也與 Hashimoto's thyroiditis 有關.

   Criteria of a disseminated lymphoma of as being a primary extranodal type
   → a markedly enlarged thyroid，apparent thyroiditis and simultaneous presentation of the extrathyroidal disease

   Lymphoma 傾向於發在具有 thyroiditis 的 thyroid 這個可能性也要考慮。
2. Distinguishing follicular lymphoma of the thyroid (with lymphoepithelial lesions) from a MALT lymphoma (with follicular colonization)

   兩者在 microscopic features 的相似處：interfollicular expansion and prominent lymphoepithelial lesions

follicular lymphoma 的病例→ underdiagnosed，被認為是 MALT lymphoma

Whether extranodal follicular lymphoma (FL) a unique entity?
沒有達成結論
(1) a series of 22 patients with FL presenting in the thyroid.

A. immunohistochemistry
CD10(+) (16/22)
surface enzyme of early lymphoid cells，common marker for ALL、Burkitt lymphoma 與 follicular centre cell lymphoma
Bcl-6(+) (22/22)
Bcl-2(+) (9/22)

B. Gene
IGH/BCL2 translocation (11/22)
→t(14;18)(q32;q21) chromosome translocation imparting the rearrangement and overexpression of the *bcl*-2 gene (IGH/BCL2 + → Bcl-2 +)
BCL6 translocation (2/12)

Classic FL：CD10(+)、Bcl-6(+)、IGH/BCL2 translocation(+)

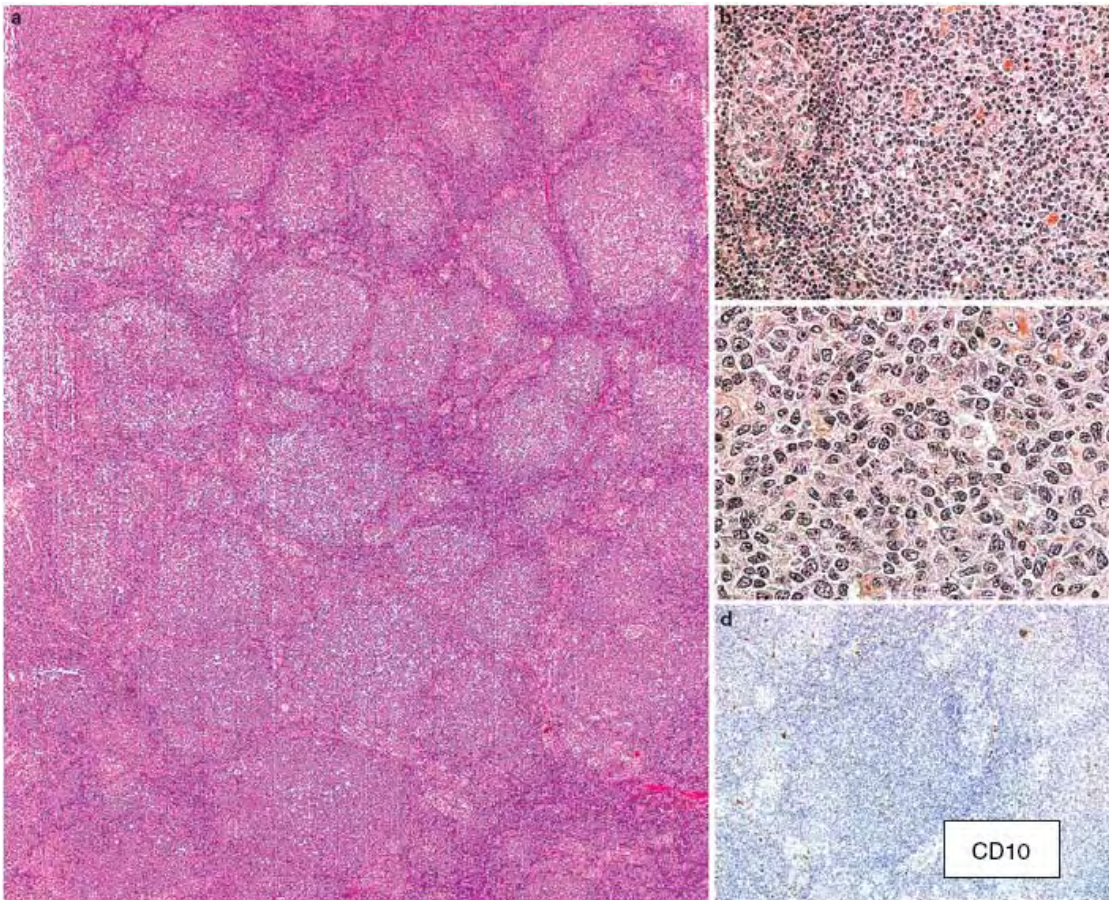
(2) Discussion

A. Bcl-2(-)與 IGH/BCL2 translocation(-) → 與 nodal follicular lymphoma 相較，更常出現在 cutaneous 與其它 extranodal FL，GI primary FL 則相反，通常為 Bcl-2(+)。

B. 因為 Bcl-2(-)、gene translocation (-)、stage IE disease 以及 a good clinical outcome 等發現，再加上 morphological features 使得一些學者認為這些 lymphoma 至少有一部份(a subset) 更像 MALT lymphoma。這些 cases 可能是 part of a separate and distinct entity，但這種分類又會使得某些病例的分類變得矛盾。

C. CD10(-) 在其它的 extranodal FL 是不尋常的，但 CD10(+)也不是 follicular centre cell lymphoma 特有的表現，曾有 CD10(+) MZBCL 被報告過，包括一個 thyroid MZBCL 的病例，Bcl-6(+)在 MALT lymphoma 中也不是被預期會出現的 finding，雖然沒有達成共識，但典型 CD10(+)、IGH/BCL2(+) extranodal FL can closely resemble MALT lymphomas 這個現象已是 well-documented。

(5) CD10(+) thyroid DLBCL 佔本篇報告所 review 的 thyroid DLBCL 約一半，其中一半具有 IGH/BCL2 translocation，這顯示 thyroid DLBCL 中有一 subset 為 germinal center cell type。



1. Lymphoepithelial lesions(LELs) and MALT lymphoma

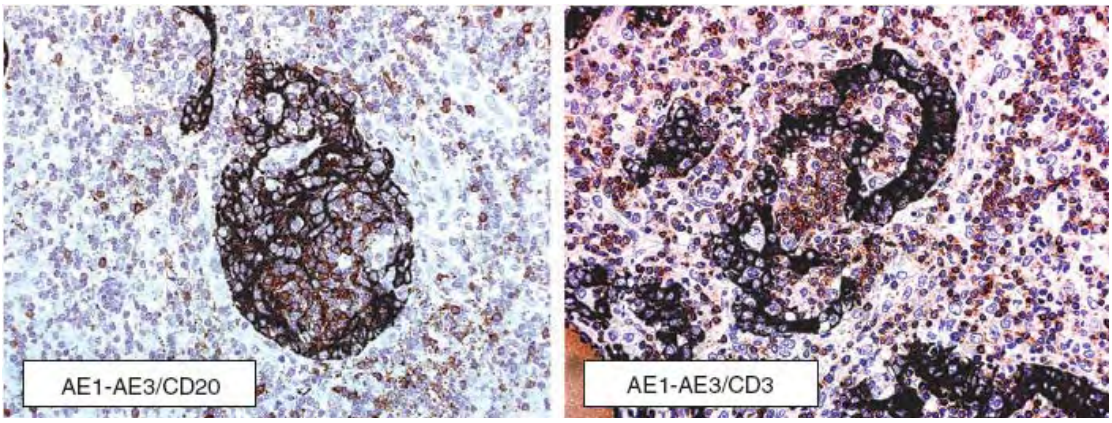
LELs 並非 MALT lymphoma 所特有的特徵，即使 LELs 出現在 DLBCL 中，也不會使之變成"MALT type"。LELs 除了是 Hashimoto's thyroiditis 的一部份之外，也會出現在各種 B-cell 甚至 non B-cell lymphoma 中。

LELs present in MALT lymphomas

(1) LEL demonstrating thyroid follicles stuffed with lymphoid cells (MALT balls) and large LELs -> characteristics of MALT lymphoma，and 也出現在一些 T-Cell lymphoma

(2) More like those seen in the salivary gland without intra-acinar balls of neoplastic lymphoid cells

(3) 與 B-cell 有關，若出現 a paucity of B cells，則 MALT lyphoma 就可被排除。Hodgkin's lymphoma 中的 LELs 會出現許多 B-cells



LELs in Hashimoto's thyroiditis → predominantly associated with T-cell，rare small B-cells. LELs 與 MALT lymphomas 兩者可能會很難以區分，利用 genotypic study 是否可行→文獻中的結果並不一致。Hsi et al 與其它研究發現 Hashimoto's thyroiditis 完全沒有 B-cell clones，但最近應用 PCR 的研究則顯示少部份具有 B-cell clone

2. Chromosomal abnormalities →t(3;14)(p14.1;q32),與 IGH 和 FOXP1 兩個 gene 有關，在其它的 MALT lymphoma 中約 10%，在 thyroid MALT lymphoma 中，有一研究發現有 50% (3/6)出現了這項異常。

Lymphomas at other extranodal sites

The Workshop

(1) 共選了 21 個發生在不尋常位置的 B-cell lymphomas 病例來討論，包括 bone、brain、lung、salivary glands、tonsil、prostate、breast、ovary 與 uterus。

(2) 選擇的標準為

a. histological classification、

b. uncommon location、

c. differential diagnosis between lymphomatous and non-lymphmatous lesions

d. discrimination of subgroups and entities with histological、clinical 與 prognostic importance.

1. CNS

(1) primary small lymphocytic lymphomas of CNS：rare

(2) primary lymphoplasmacytic lymphomas of CNS：extremely uncommon in such case → 應先考慮 secondary infiltrations by systemic lymphoplasmacytic lymphoma(Bing and Neel syndrome)，或 meningeal MALT-type lymphoma

2. Bone

Hairy cell leukemia 會產生 secondarily osteolytic and tumorous lesions，但在 hairy cell leukemia 發展出典型的血液學特徵之前，就先產生 osteolytic and tumorous lesions 的情況非常罕見，腫瘤細胞對 cyclin D1 與 annexin 1 呈現 positive 有助於對這類 hairy cell leukemia 的病例與其它 bone marrow lymphomas 進行 differential diagnosis。

名詞解釋

Hairy cell leukemia

(1) chronic lymphoid leukemia，B-cell disease
(2) 血液學特徵：excessive abnormal B-cell with hairy appearance
(3) 免疫化學特徵：over expression of cyclin D1 and annexin 1

Cyclin D1 – a cell-cycle regulator(G1 -> S phase); a cofactor of transcription

Annexin 1 – a member of annexin family，able to bind (i.e. to annex) to cellular membranes in a calcium-dependent manner，a phospholipase A2 inhibitory protein，also inhibitory to iNOS and COX-2 enzyme，促進 inflammatory cell apoptosis，總之 → anti-inflammation

3. Burkitt lymphoma(Burkitt's lymphoma) restricted to one organ (abdominal organ: liver prostate etc.) → very rare
   正確的診斷必須要根據 morphological、immunohistochemical 以及 molecular criteria，因為這類疾病在適當治療後可能有較佳的結果。

名詞解釋

Burkitt lymphoma – NHL，B cell lymphoma，"starry sky" histological features

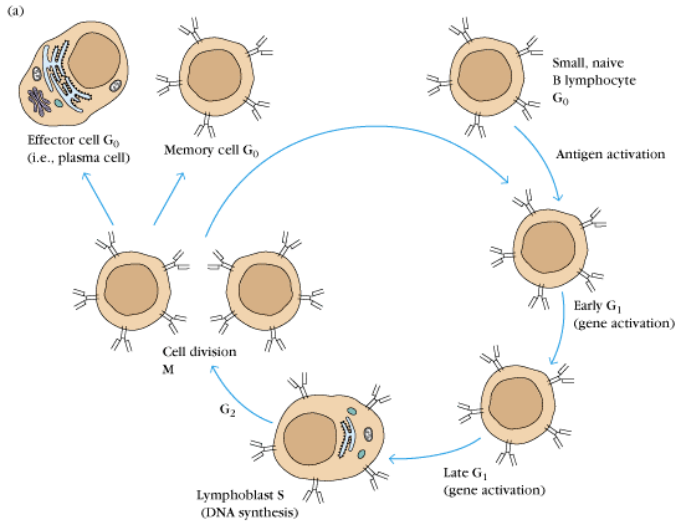
(1) African – involve jaw and abdomen
(2) American(other area except central Africa) – involve bone marrow and abdomen

4. primary extranodal, extracutaneous FLs – rather infrequently
   (1) 除了 GI FLs 之外，其它的 FLs 在 microscopic、immunohistochemical 與 molecular features 都與 nodal FLs 不同，大部份為 Bcl-2(-)與 t(14;18) (-)。
   (2) 有一些部位的 FLs 需要考慮成為一個單獨分開的 subgroups，例如發生在兒童時期的 testicular FLs，因為這類 FLs 在 simple surgical resection 之後似乎有很好的 outcome，有一些類似的 cases 也發生於成人。

Large B-cell lymphomas of terminally differentiated B-cells

B cell development、activation and maturation

The Cell Cycle of B lymphocytes



small B cell →^{Ag} centrocyte → centroblast → B immunoblast
(large, cleaved) (large, noncleaved) (large)
|
→ plasma cell

mature B-cell：CD20(+)
plasma cell：CD38(+), CD138(+)

1. Plasmacytic lymphoma ：a variant of diffuse large B-cell lymphoma
   (1) Proliferation of immunoblastic B cell
   (2) CD20 為 negative 或 weak positive
   (3) Plasma cell-associated antigen(CD38，CD138)為 positive
   (4) 主要在 HIV(+)的病人身上診斷出來
   (5) clinical behavior：aggressive with poor response to therapy and short survival
2. 數份研究發現其它具有類似 morphological 與 phenotypic plasmablastic 特徵的 lymphoma，但臨床與分子特徵並不相同，這表示他們可能是不同的 disease entities。

Plasmablastic lymphoma
1. 特色：

(1) Proliferation of large B cell with immunoblastic morphology and plasma cell immunophenotype

(2) a cohesive pattern of growth and a monomorphic appearance

2. 好發對象：mainly diagnoses in HIV(+) p'ts

3. 3 cases in the Workshop

(1) CD20(-)、CD79a(-)、plasma cell associated antigens(+)、EBV(+) with type I latency pattern

(2) Also containing a range of cells with plasmacytic differentiation

→ plasmablastic lymphoma with plasmacytic differentiation (Colomo et al)

(3) Presented in extra-nodal site other than oral mucosa

(4) One case have low M-spike(M protein，Bence Jones protein，multiple myeloma 會產生) and bone marrow involvement

→ 顯示 plasmablastic lymphoma 可有 extensive bone involvement 與 minimal M component，然而其臨床與病理組織特徵皆與 multiple myeloma 不一致。

4. Clinical behavior：Aggressive，recent reports → 以 HAART 來治療可有 better outcome

Primary effusion lymphomas and extra-cavitary primary effusion lymphoma variant

1. 好發對象:對象常在有 HHV-8 及 EBV infection 的 immunosuppressed patients 看到
2. 特徵：有大量 pleomorphic B cells 的增生
3. 免疫化學特色：缺乏 B cell marker 的表現，常表現出 plasma cell-associated antigens and CD30。
4. Tissue involvement：PEL 通常無 tissue involvement，然而有些病例可能會發展出 a solid tissue mass and 繼而發展出 a cavitary lymphomatous effusion
5. 好發位置：extra-cavitary variant 常發生在 lymph nodes、lung、skin and GI tract，偶爾發生在 oral mucosa 與 larynx。
6. One of the cases presented in the Workshop：a HHV+ nodal large cell lymphoma with plasmablastic features that subsequently developed a GI mass and tumoral ascities
7. Studies review：

(1) 數份研究發現一種 pure extracavitary variant of PEL，有 solid tissue mass 卻缺乏 evidence of malignant effusions.

(2) 這個 variant 具有與 PEL 類似的 morphological、immunophenotypic 與 molecular 特徵，顯示它們屬於同一 entity

(3) 其 extracavitary presentation 同樣會侵犯 skin、GI tract 與 lymph nodes。

(4) 特色：具有 phenotypic peculiarities

a. a slightly more frequent expression of mature B-cells markers (CD20) and immunoglobins

b. 偶爾表現 T-cell associated markers 與 less EBV positivity

c. 這種 solid variant of PEL 的病人較少發生伺機性感染，這種較好的結果可能是因為 HIV+病人以 HAART 治療導致 better control of HIV and improvement of CD4 counts。

Extramedullary plasmablastic tumours secondary to plasma cell neoplasms

1. plasmablastic lymphoma，特別是具有 plasmacytic features 的 cases 與 extramedullary large cell transformation of plasma cell neoplasma 擁有類似的 morphological 與 phenotypical 特徵，若無 clinical correlation，兩者難以區分
2. 大部份 transformation of extramedullary plasmacytomas 或 extramedullary dissemination of multiple myeloma 都是在最初診斷數年後才發生(as secondary evolution of these diseases)，有一些會在最初診斷時就同時出現。
3. One of the cases in the Workshop： an extranodal large B-cell neoplasm with plasmablastic features 在診斷後兩年，經 chemotherapy 治療完全 remission 後，進展為 overt multiple myeloma。這說明兩者之間 differential diagnosis 的困難。
4. 臨床上：extramedullary plasmablastic tumours secondary to plasma cell neoplasms 發生在 immunocompetent patients，而 plasmablasitc lymphoma 好發於 immunosurressed patients。
5. Phenotypically: 兩者類似，前者較易有 CD56 expression，cyclin D1+ 只在 MM 病人偵測到。

5. EBV infection: 在 plasmablastic lymphoma 病人常見，在 plasma cell neoplasm 的病人則為 negative。

Other large B-cell lymphomas with plasmablastic features

DLBCL with ALK+

1. 具有 anaplastic lymphoma kinase (ALK) 的 DLBCL may correspond to a distinct disease in this spectrum of neoplasms.
2. 好發位置與對象：Usually nodal and present in young immunocompetent pateients
3. 特色：proliferation of B cells，EBV-，具有 plasmablastic phenotype 以及 frequent expression and secretion of IgA
4. ALK expression：與 anaplastic large cell lymphma 類似，ALK 的表現是因為 ALK 的 rearrangement。
5. Clinical behavior：aggressive，most patients die in a short time。

HHV-8+ large B-cell lymphoma emerging context of multicentric Castleman’s disease

1. Phenotypical features：strongly CD20+，EBV-
2. 好發對象：immunocompetent patient
3. a variant of DLBCL at a more mature terminal stage of differentiation than plasmablastic lymphoma。

Table 4. Diffuse large B-cell lymphomas (DLBCL) with terminally differentiated B-cell phenotype

Plasmablastic lymphomas (PBL)
Plasmablastic lymphoma of oral mucosa type
Plasmablastic lymphoma with plasmacytic differentiation
HHV-8-associated lymphomas
Plasmablastic lymphoma associated with multicentric Castleman's disease*
Primary effusion lymphoma (PEL)
Extracavitary variant of PEL
Extramedullary plasmablastic tumours secondary to plasma cell neoplasms
Diffuse large B-cell lymphoma expressing ALK
*Differential diagnosis**
Diffuse large B-cell lymphoma with secretory differentiation
Pyothorax-associated lymphoma

*These tumours express strong CD20 and therefore are probably better designated as immunoblastic variants of diffuse large B-cell lymphoma.

Other lymphoproliferative disorders in immunocompromised patients and EBV-related lymphomas

1. WHO classification：Immunodeficiency-associated lymphoproliferative disorders(IDA-LPDs)
2. Four categories：
   (i) associated with primary immune disorder(PID)
   (ii) associated with HIV infection
   (iii) post-transplant
   (iv) methotrexate-associated
3. Cases in the Workshop
   (1) 13 cases including
      (i) PTLD
      (ii) Patients with autoimmune disorders treated with methotrexate
      (iii) patients with a previous lymphoma treated with chemotherapy
      (iv) associated with EBV infection without clinical evidence of

immunosuppression

HIV+ cases 已在 plasmablastic lymphoma section 中討論。

這些 cases 表現出 IDA-LPDs 可能出現的各種 clinical situations，其中不只包括 well-known conditions，也包含 autoimmune disorders、methotrexate or other immunosuppressive treatment，haematological neoplasmas and newly emerging phenomena，例如 senile LPD。事實上，LPD 可能與一或多個 underlying viral infections 有關，例如：EBV。

(2) 這些 cases 表現出 heterogeneous pathological manifestations，包括 overt malignant lymphomas，polymorphic proliferations 以及 lesions of uncertain biological significance that are not different from those observed in nodal disorder. 其中三個 PTLDs 的病例表現出 plasmablastic/plasmacytic differentiation，與之前所討論的 large B-cell lymphoma with plasmablasitc features 類似。

(4) 有一半的 PTLD cases 為 EBV-而且傾向比 EBV+更晚發生。

Mucosa-associated lymphomas

3 conditions including 2 major types(1 & 2)：

1. extranodal MZBCL of mucosa associated lymphoid tissue(MALT) –
   (1) 通常發生在胃的 mucosal lymphoid tissue，
   (2) acquired usually as a reaction to Helicobacter pylori
   (3) indolent clinical course
2. Enteropatho-type T-cell lymphoma(ETCL)
   (1) derived from intestinal intra-epithelial T cells
   (2) often evolving as a consequence of adult-onset celiac disease with rapidly fatal outcome
3. atypical marginal zone hyperplasia of MALT，described most recently， occur in tonsil or appendix in childhood.

本段主要焦點在 extragastric MALT lymphoma，因此 gastric lymphoma 就被排除了。

Extragastic MALT lymphoma

1. 好發位置：ocular adnexa、salivary gland、skin、lung、intestine、thyroid and breast。除了這些常見的位置，Workshop 的 cases 還包括罕見的位置：thymus、subcutaneous tissue、 dura 與 larynx，這顯示沒有器官或組織不能產生這類的 marginal zone B-cell-related neoplasia。
2. 微生物：最近的研究報告指出可能與 infectious agent 有關，
   (1) Cutaneous lesions：Borrelia burgdorferi
   (2) MALT lymphoma of ocular adnexa：Chlamydia psittaci

(3) Intestinal MALT lymphoma(immunoproliferative small intestinal disease，IPSID)：Campylobacter jejuni

這些微生物與 MALT lymphoma 的關係並不像 H. pylori 如此 straightforward

3. Histological appearance：markedly influenced by local environment 與 underlying inflammatory/autoimmune。MALY lymphoma 不同病例間其腫瘤細胞的 cytomorphology 可能會有差異，即使在同一腫瘤也會有差異，由 small lymphoid cells 至 centrocyte-like cells and monocytoid cells，non-neoplastic germinal centres 或 colonized remnants。

4. The frequency of LELs at mucosal sites

與發生的位置有關，並反應了 the interaction between lymphoma cells and epithelial structures。

(1) Thyroid：invariably
(2) Salivary glands and lung：often seen
(3) Ocular adnexa：rarely encountered，特別是 lacrimal gland、intestine and breast
(4) Cutaneous：exceedingly rare to absent

LELs are neither specific for MALT lymphoma nor required for the diagnosis.

5. 特徵：

(1) derives from postgerminal centre memory B cell → up to 30% extragastric MALT lymphoma 具有 plasmablastic differentiation。
(2) often associated with serum paraproteinaemia
(3) small groups of light chain restricted lymphoplasmacytoid cells or plasma cell (usually containing IgM) 會表現出 intranuclear PAS + material (Dutcher bodies)

6. Differential diagnosis

要考慮 small B-cell lymphocytic proliferations，mantle cell lymphoma 與 follicular lymphoma。

7. Immunohistochemistry

(1) 大部份的 cases 為 CD20+、CD5-、Bcl-6-、CD10-、CD23-
(2) these cells colonize reactive germinal centers which display a disrupted network of CD21+ follicular dendritic cells。
(3) MALT lymphoma 並沒有 highly characteristic marker，少數 cases 表現 CD5+，有一些則表現出 CD43+
(4) Nuclear Bcl-10 在 t(1;14)(q22;q21)+的 cases → strong
在 t(11;18)(q21;q21)+的 cases → moderate

8. Molecular and genetic biology

(1) 對MALT lymphoma 有specific的structural aberrations主要為下列三種：,
→ t(11;18)(q21;q21), t(1;14)(q22;q32) and t(14;18)(q32;q21)

最近的研究出現了第四種→t(3;14)(p14.1;q32),
這四種genetic aberrations的occurrence 受到lymphoma發生位置的影響

a. t(11;18)(q21;q21) -- detected in gastric (24%) and pulmonary tumours (50%)
b. t(14;18)(q32;q21) – detected in ocular adnexal /orbitalMALT lymphomas (24%)
c. t(3;14)(p14.1;q32) -- detected in three of six thyroidal MALT lymphomas and in 20% of ocular adnexal / orbital tumours.
d. t(1;14)(q22;q32) – very rare, largely restricted to pulmonary and gastric lesions.

t(11;18)(q21;q21)常用reverse transcriptase (RT)-PCR技術來檢測，其他三項則是使用fluorescence in situ hybridization(FISH)。

(2) Numerical aberrations → such as +3, +12 and +18,
可單獨發生也會與structural aberrations一起合併發生，除了一個t(11;18)(q21;q21)的case以外。trisomy 3 常發生在intestinal, salivary gland and ocular adnexal tumours的cases

Table 5. Frequencies (%) of trisomies 3 and 8 in mucosa-associated lymphoid tissue lymphomas of different sites[45]

	n	Trisomy 3	Trisomy 18
Stomach	71	11	6
Skin	51	20	4
Salivary gland	42	55	19
Ocular adnexa/orbit	37	38	14
Intestine	16	75	25
Lung	15	20	7

(3) translocations 與MALT lympnoma 有很強的關聯性可幫助診斷特定病例，例如small lung biopsy有lymphoid infiltrate且懷疑為MALT lymphoma的情況；同樣的trisomes 3 and 18與MALT lymphoma的關聯性可用來幫助診斷一些有疑慮的cases。在適當的histopathological and immunophenotypic features的背景下，偵測到這些genetic aberrations將強烈傾向MALT lymphoma的診斷因此FISH and RT-PCR是比immunoglobulin gene rearrangement studies by PCR更powerful的工具。目前仍無任何証據險示這些genetic aberrations具有臨床重要性，最後的結論仍有待大型研究結果。因為MALT lymphoma常侵犯多重位置，因此在確立診斷後，完整的staging是非常重要。

Enteropathy-type T-cell lymphoma

ETCL的診斷是困難且有挑戰性的，特別是small endoscopic biopsies 的cases以及有大量inflammatory infiltrate蓋過lymphoma component的病例，在診斷為ETCL前，常會被診斷為refractory coeliac disease 在這種背景下，duodenal biopsies 會有下列特色

(1) Villous atrophy
(2) A marked increase of cytologically normal, but immunophenotypically abnormal intraepithelial lymphocytes (IELs),
(3) Usually characterized by loss of CD8.
(4) IELs are monoclonal by PCR.

會出現multiple flat intestinal ulcers，稱為ulcerative jejunitis，其中含有一些cytologically transformed cells，這些細胞可能很難以顯微鏡偵測到。
這些 immunophenotypically abnormal monoclonal IELs的累積是產生ETCL的第一步 → Patients with refractory coeliac disease and /or ulcerative jejunitis are therefore suffering from a neoplastic T-cell disorder，範圍可能涵蓋大部份GI tract。

Atypical marginal zone hyperplasia of MALT
MALT lymphomas通常發生在acquired MALT，很少出現在native MALT 例如tonsil and Peyer's patches.這類indolent lymphomas 由immunoglobulin light-chain restriction 以及CD43異常的expression(in some cases)的特徵所推論發現，最近的研究發現重大的例外，並且也列入Workshop的討論。6個marginal zone hyperplasia侵犯tonsil與appendix 的病例被提出，具有下列特徵

(1) Expansion of the marginal zone by centrocyte-like and transformed cells
(2) Heavily spilling into the tonsillar crypt epithelium mimicking MALT lymphoma.
(3) Immunophenotypically, these cells showed k light-chain restriction and CD43 expression; however, comprehensive molecular studies convincingly failed to show any evidence of monoclonal immunoglobulin gene rearrangement in any of the six cases.

臨床追蹤這六個案例並沒有復發，平均追蹤時間將近三年。

Anaplastic large-cell lymphoma and its differential diagnosis

1. Anaplastic large-cell lymphoma is a pleomorphic large cell lymphoma with strong expression of the activation antigen CD30 in virtually every cell and frequent involvement of lymph node sinuses. A
2. 好發年齡：(1) Predominantly in children and young adults
   (2) A second peak incidence in 60–80-year-olds.
3. Pathogenesis：dysregulation of the receptor tyrosine kinase gene ALK on chromosome 2p23 對anaplastic large-cell lymphomas的形成很重要。Expression

of ALK與 young age, systemic disease, a cytotoxic epithelial membrane antigen (EMA)+ phenotype 以及好的預後有關。

4. 比例： anaplastic large-cell lymphoma 佔所有lymphoma的2-3%
   其中約 40–65%的cases有extranodal disease，不論是primary或是secondary(as part of a systemic process)
5. 位置：skin (15–30%), bone (5–20%), liver (5–10%), lung (5–15%), soft tissue (10–20%), muscle (< 5%) and rarely (< 1%) gut, testis, parotid, thyroid, breast, pancreas, oral cavity and ocular adnexa.
6. Differential diagnosis of CD30+infiltrates -- 下列診斷都需要考慮
   (1) reactive processes
   (2) large cell neoplasms

正確診斷anaplastic large-cell lymphoma 是很難的，特別是 extranodal sites，因為其它的lymphoma更常見。決定腫瘤侵犯的範圍((primary versus systemic process)同樣十分重要，特別是發生於skin 的cases。Workshop所討論的100個cases中有8個cases的診斷或鑑別診斷為anaplastic large-cell lymphoma，這些cases顯示ALK expression 並不一定與systemic disease及good prognosis 有關，並進一步討論ALK– anaplastic large-cell lymphoma 是否distinct from peripheral T-cell lymphoma unspecified。

Morphological or immunophenotypic features that could lead to the wrong diagnosis in anaplastic large-cell lymphoma

1. 下列疾病在histological上要與anaplastic large-cell lymphoma 作鑑別診斷：
   (1) viral infection,
   (2) drug reactions,
   (3) other lymphomas (Hodgkin's lymphoma and B-, T- and NK-cell lymphomas),
   (4) carcinoma,
   (5) melanoma
   (6) granulocytic sarcoma.
2. CD30 positivity
   上列診斷與anaplastic large-cell lymphoma都為CD30+，但pattern不同
   (1) Other disease,
      a. often present in only a subset of cells
      b. weak and focal or diffuse staining
      c. cytoplasmic pattern
   (2) anaplastic large-cell lymphoma
      a. Virtually every cell in anaplastic large-cell lymphoma.
      b. Strong and diffuse pattern

c. Golgi CD30+

3. anaplastic large-cell lymphoma與carcinoma之區別

具有下列特徵的lesion將指向標題所列的兩個方向，

(1) the cohesive growth pattern,

(2) lack of leucocyte common antigen (CD45RB) in up to 38%,

(3) frequent EMA expression,

(4) null phenotype (10–20% of cases),

(5) rare keratin expression

如同Workshop所討論的一個case(a CD30+ large pelvic mass in a 37-year-old female with all these features). 但ALK+以及 lack of ultrastructural features of an epithelial malignancy 兩項特點使得診斷可以確認為anaplastic large-cell lymphoma。

4. ALK expression

對ALK– anaplastic large-cell lymphoma with a null phenotype, 完整的 immunophenotyping, clinical staging and ultrastructural studies 對確認診斷是必須的檢查。ALK的表現不可當作診斷anaplastic large cell lymphoma唯一依據，因為其它的腫瘤也會呈現ALK+，例如inflammatory myofibroblastic and other soft tissue tumours, tumours of neural origin (neuroblastoma, glioblastoma) and a very rare ALK+ B-cell lymphoma.

5. Expression of myeloid antigens (CD13 and rarely CD117)

在anaplastic large-cell lymphoma 很少見而且可能造成誤解，如同Workshop中一個35歲女性 with a parotid mass的病例，

(1) Fine-needle aspiration -- expression of HLA-DR and CD13
lack of CD2, CD3, CD4, CD8,

→ suggesting the diagnosis of chloroma.

(2) Excisional biopsy and paraffin immunoperoxidase studies -- CD30+, EMA+, ALK-1+

→ the correct diagnosis of anaplastic large-cell lymphoma was made.

所以在CD13+ cases, 必須小心排除myeloid process

ALK expression in anaplastic large-cell lymphoma as a determinant of systemic disease and prognosis

1. General rule：ALK+ →與systemic disease and a better prognosis 有關
2. Skin

(1) the most common location of extranodal anaplastic large-cell lymphoma

(2) cutaneous anaplastic large-cell lymphoma

Primary type：indolent，disease related 5-year survival of > 90%

Skin involvement in systemic disease：5-year survival of < 45%.

(3) Treatment

Primary type -- conservative with resection with or without irradiation;
low-dose methotrexate is used in multifocal disease not amenable to localized therapy.

Systemic anaplastic largecell lymphoma with skin involvement
--requires multiagent chemotherapy.

At the present time, there are no reliable biological markers

(4) Biological marker for staging (primary vs systemic)

No reliable biological marker to distinguish the two types of anaplastic large-cell lymphoma.

a. ALK

Most primary cutaneous anaplastic largecell lymphomas → ALK–
systemic disease with multiple skin involvement → ALK +

例外的case – a 26-year-old male, rare cases of well-documented primary cutaneous anaplastic large-cell lymphoma are ALK+

ALK-並無法排除systemic disease，有20–60%of anaplastic large cell lymphomas為ALK–.。

b. EMA

如同ALK，EMA+較常出現在systemic systemic anaplastic large-cell lymphoma with secondary skin involvement
primary – 32%
systemic – 67%

例外的case：primary cutaneous anaplastic large-cell lymphoma with ALK– but EMA+

EMA expression cannot be used reliably to stage cutaneous anaplastic largecell lymphoma. If present，EMA expression could be used to distinguish anaplastic largecell lymphoma from other reactive CD30+ cutaneous infiltrates (bug bites, drug reactions, viral infections, etc.).

c. Clusterin

最初被認為只在systemic anaplastic large-cell lymphoma表現，但最近的研究發現有41%-100% of primary cutaneous anaplastic large-cell lymphomas也會表現clusterin.

(5) Prognosis

a. systemic ALK+ anaplastic large-cell lymphoma have a favourable prognosis compared with the ALK– group.

例外：Patients with ALK+ tumours at extranodal sites, particularly the bone, 並不永遠有a good prognosis.

b. 其它 poor prognostic factors 包括 small cell variant histology and peripheral blood involvement and CD56 expression.

2. CNS

(1) Primary CNS anaplastic large-cell lymphoma – very uncommon, less than 20 cases.

(2) ALK+ primary CNS anaplastic large-cell lymphomas (approximately 50%) → a better prognosis.

(3) An unusual feature of primary CNS anaplastic large-cell lymphoma is the high degree of involvement of the dura or leptomeninges (69%)

(4) 例外的case：A CD56+, ALK+, t(2;5)(p23;q35)+, primary brain anaplastic large-cell lymphoma in a 27-year-old immunocompetent male 儘管為ALK+ , the patient had an aggressive course possibly related to CD56 expression by the tumour cells.

(5) ALK is weakly positive in normal glia, neurons and endothelial cells in the CNS，這點對決定ALK positivity in brain anaplastic large-cell lymphoma並不構成問題。.

(6) ALK is expressed in neuroblastoma and glioblastoma, but these tumours are CD30–.

How to classify ALK- anaplastic large-cell lymphoma

1. Approximately 20–60% of anaplastic large-cell lymphomas →ALK–.
除了primary cutaneous anaplastic large-cell lymphoma之外，其它anaplastic large-cell lymphomas 缺乏of a defined common pathogenic mechanism or specific clinicopathological features 因此haematopathologists have debated whether the diagnostic criteria for ALK– anaplastic large-cell lymphoma define a specific entity or if ALK– anaplastic large-cell lymphoma should be included in peripheral T-cell lymphoma unspecified.
2. Three ALK–, CD30+ non-cutaneous T-cell lymphomas in the Workshop.

(1) Case 1 -- a lung lesion , CD30+ in a subset of the cells and an angiocentric growth pattern，腫瘤細胞表現 CD4+, CD5+ 但缺乏EMA, TIA-1, CD56 與 EBV 表現

→ the diagnosis：CD30+ peripheral T-cell lymphoma unspecified.

(2) Case 2 – expressed CD15 and CD30

→ the differential diagnosis：Hodgkin's lymphoma
CD15+ anaplastic large cell lymphoma
CD15+, CD30+ peripheral T-cell lymphoma

(3) Case 3 -- a rare presentation of T-cell anaplastic large-cell lymphoma arising in the soft tissue around a breast implant in a 49-year-old female.
Anaplastic large-cell lymphoma in the breast → rare，不論primary或secondary，.以前的報告中大約35%發生在breast的anaplastic large-cell lymphomas 起源與prosthetic implants有關，而且在與breast implant相關的lymphma 中，anaplastic large cell lymphoma 佔了至少50%的cases

3. 主要的討論重點在ALK– anaplastic large-cell lymphoma 是否為 a distinct entity. 或是要歸類為peripheral T-cell lymphoma unspecified. genomic hybridization studies發現它們具有不同的特色。
(1) 兩者皆有的chromosomal alterations -- such as loss of 6q and 13q
(2) 在T-cell lymphoma unspecified 中較常見
Loss of 9p21-- 31% in peripheral and 0% in anaplastic large-cell lymphoma
Loss of 5q21 -- 33% in peripheral T-cell lymphoma unspecified versus 0% in anaplastic large-cell lymphoma
(3) 在ALK– anaplastic large-cell lymphoma 中較常出現
Gains of chromosome 1q -- 46% versus 17%
(4) 此外，與ETCL, T-prolymphocytic leukaemia and adult T-cell leukaemia /lymphoma相較，both the two tumors 擁有與它們不同的genetic differences
(5) Losses of 5q and 12q also appear to segregate peripheral T-cell lymphoma unspecified from other well-defined T-cell lymphomas.
(6) Chromosome 2
a. Extra copies of chromosome 2p23 出現在ALK– anaplastic large-cell lymphoma 與primary cutaneous anaplastic large-cell lymphomas的cases, 但ALK+ anaplastic large-cell lymphomas則無
b. imbalances in chromosome 2 in five (26%) of nodal/systemic anaplastic large-cell lymphomas (one ALK+, four ALK–) and no primary cutaneous anaplastic large-cell lymphoma.
c. solitary amplifications of 2cen-p22 or imbalances of chromosome 2 in 15/ 42 (31%) of peripheral T-cell lymphoma-NOS.
Extra copies of chromosome 2 are not uncommon in lymphoma and have been reported in B- and T-cell lymphoma and Hodgkin's lymphoma
(7) A defect in T-cell receptor (TCR) ab protein expression (using antibody bF-1) has been identified in >90% of ALK+ and ALK– anaplastic large-cell lymphomas，only approximately 10% of peripheral T-cell lymphoma unspecified

and no angioimmunoblastic T-cell lymphomas (AILT).

(8) Ninety-six percent of ALK+ and 40% of ALK– anaplastic large-cell lymphomas also lacked expression of the CD3 antigen, compared with 29% of peripheral T-cell lymphomas NOS and 20% of AILT.

CD3 之功能：associated with the TCR protein and transduce the signal of TCR engagement to ZAP-70, a tyrosine kinase that integrates cognate and costimulatory signals for downstream signalling.

(9) ZAP-70

As further evidence of a defect in TCR signalling, ZAP-70 is lost in anaplastic large-cell lymphoma compared with other T-cell lymphomas. Overall, ZAP-70 is detected in 25–30% of anaplastic large-cell lymphomas (8–25% of ALK+ and 20–41% ALK–) versus 59–74% peripheral T-cell lymphomas NOS and 29–57% of primary cutaneous (PC) anaplastic large-cell lymphomas.

(10) Clusterin

Virtually all (82–100%) systemic anaplastic largecell lymphomas, including ALK+ and ALK– cases, and 41–100% of primary cutaneous anaplastic large-cell lymphomas express clusterin, a ubiquitous glycoprotein encoded by a gene on chromosome 8p21.

Clusterin 之功能： including complement regulation, cell aggregation, lipid transport and response to cell injury or stress.

Clusterin is expressed in a Golgi associated pattern in anaplastic large-cell lymphoma. In contrast, clusterin is present in only 3.5% of peripheral T-cell lymphoma unspecified cases from three series and only 13% of other T-cell neoplasms were positive and usually showed a more diffuse cytoplasmic staining rather than the more distinct Golgi pattern of reactivity seen in anaplastic large-cell lymphoma.

(11) Microarray analysis

Recent microarray analysis of ALK+ and ALK– anaplastic large-cell lymphoma (including primary cutaneous anaplastic large-cell lymphoma) has shown ALK+ compared with ALK– anaplastic large-cell lymphoma over-expresses genes encoding signal transduction molecules (SYK, LYN, CDC37) and underexpresses transcription factor genes (including HOXC6 and HOX A3). Both groups highly expressed kinase genes (LCK, protein kinase C, vav2 and NKIAMRE) and antiapoptotic molecules, suggesting overlap in pathogenesis; a comparison with peripheral T-cell lymphoma unspecified was not performed in this study.

4. Conclusion

(1) Recognition of the t(2;5) and abnormal expression of ALK in lymphoid tissue have further clarified our understanding of anaplastic large-cell lymphoma and helped in its diagnosis, particularly at extranodal sites or where other antigens may be expressed.

(2) ALK expression is usually associated with systemic disease and a better prognosis, but there are important exceptions. ALK expression can rarely be seen in anaplastic large-cell lymphoma limited to the skin; there is currently no substitute for careful staging and follow-up. In ALK+ anaplastic large-cell lymphoma other factors such as CD56 may indicate a poor prognosis.

(3) The classification of ALK– anaplastic large-cell lymphoma is controversial. Current genetic and biological features provide evidence that ALK– anaplastic large-cell lymphoma is more closely related to ALK+ anaplastic large-cell lymphoma than peripheral T-cell lymphoma unspecified and strongly support inclusion of ALK– CD30+ lymphomas with anaplastic large-cell lymphoma in future lymphoma classification.

(4) To make a diagnosis of ALK– anaplastic large-cell lymphoma there must be strict adherence to characteristic cytology (a large cell predominant population with abundant cytoplasm and pleomorphic, embryo or hallmark nuclei or wreath-like giant cells) and strong CD30 expression with a membrane and Golgi distribution in virtually every cell. In lymph nodes, some involvement of sinuses should be seen. In ALK– anaplastic large-cell lymphoma with a null phenotype (and genotype), immunostains to exclude other tumours such as Hodgkin lymphoma (HL), carcinoma and acute leukaemia must be performed.