Early lymphoid lesions: conceptual, diagnostic and clinical challenges

Karthik A. Ganapathi,[1] Stefania Pittaluga,[1] Oreofe O. Odejide,[2] Arnold S. Freedman,[2] and Elaine S. Jaffe[1]

[1]Hematopathology Section, Center for Cancer Research, Laboratory of Pathology, National Cancer Institute; and [2]Center for Hematologic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA

ABSTRACT

There are no "benign lymphomas", a fact due to the nature of lymphoid cells to circulate and home as part of their normal function. Thus, benign clonal expansions of lymphocytes are only rarely recognized when localized. Recent studies have identified a number of lymphoid proliferations that lie at the interface between benign and malignant. Some of these are clonal proliferations that carry many of the molecular hallmarks of their malignant counterparts, such as BCL2/IGH and CCND1/IGH translocations associated with the *in situ* forms of follicular lymphoma and mantle cell lymphoma, respectively. There are other clonal B-cell proliferations with low risk of progression; these include the pediatric variants of follicular lymphoma and marginal zone lymphoma. Historically, early or incipient forms of T/NK-cell neoplasia also have been identified, such as lymphomatoid papulosis and refractory celiac disease. More recently an indolent form of T-cell lymphoproliferative disease affecting the gastrointestinal tract has been described. Usually, $CD8^+$, the clonal cells are confined to the mucosa. The clinical course is chronic, but non-progressive. NK-cell enteropathy is a clinically similar condition, composed of cytologically atypical NK-cells that may involve the stomach, small bowel or colon. Breast implant-associated anaplastic large cell lymphoma is a cytologically alarming lesion that is self-limited if confined to the seroma cavity. Atypical lymphoid proliferations that lie at the border of benign and malignant can serve as instructive models of lymphomagenesis. It is also critical that they be correctly diagnosed to avoid unnecessary and potentially harmful therapy.

Introduction

It is now accepted that most cancers are a result of the dysregulation of multiple molecular pathways. This paradigm has been proven in many solid tumors with the recognition of pre-malignant lesions that frequently precede invasive cancer. Studies of solid tumors have provided insight into the sequence of molecular alterations associated with tumor progression. However, this paradigm does not immediately extend to lymphomas, due to the innate circulatory capacity of lymphocytes, rendering the concept of "benign lymphoma" more challenging. Indeed, in contrast to epithelial and mesenchymal neoplasms, classification systems have not recognized both benign and malignant lymphomas. For many indolent lymphoproliferative disorders, the clonally expanded lymphocytes do not remain localized, but disseminate based on the patterns of normal lymphocyte homing. They also are frequently responsive to immunoregulatory signals; it is only when the proliferation becomes autonomous that features of malignancy are clearly evident. Thus, these early lesions have many of the attributes of benign neoplasms.

The expansion in knowledge of disease-specific genetic and phenotypic alterations has resulted in the detection of clonal lymphoid lesions sharing genetic and/or phenotypic aberrations with well-defined neoplasms like chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), multiple myeloma (MM), follicular lymphoma (FL) and mantle cell lymphoma (MCL) without fulfilling diagnostic criteria for overt malignancy. A second group of "indolent" and indeterminate clonal lymphoid proliferations do not have a counterpart among the currently recognized subtypes of lymphoma, but appear to have a limited potential for progression. Their optimal therapeutic management has not been clear and recent data suggest that conservative management may be sufficient in most cases. Included in this group are the pediatric variants of follicular lymphoma and nodal marginal zone lymphoma, as well as breast-implant associated anaplastic large cell lymphoma (ALCL)

These observations raise important practical and theoretical questions, some of which were addressed at a recent workshop on this subject.[1] What is the definition of "malignant lymphoma" in 2014, since neither monoclonality nor genetic aberrations equate with malignancy based on current knowledge? Clonal populations of B and T lymphocytes have been identified in many reactive or infectious disorders, and many lymphoma- or leukemia-associated translocations have been identified in the peripheral blood of healthy individuals.[2] In this review, we summarize the diagnostic criteria, recent advances in predicting progression and current recommendations for management of the more recently recognized early or indeterminate clonal lymphoid lesions of B-cell, T-cell and NK-cell derivation (Table 1). An understanding of these indolent and sometimes self-limited proliferations is critical to determine the appropriate clinical management. We have omitted discussion of lymphomatoid papulosis and the spectrum of primary cutaneous CD30-positive T-cell lymphoproliferative disorders as this topic has been covered extensively in the literature.[3] Similarly, in the interest of space, we will not discuss lymphoproliferative disorders secondary to viral transformation.[4] Diagnostic criteria for some of these early lesions were incorporated into the 2008 World Health Organization (WHO) classification of lym-

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Correspondence: ejaffe@mail.nih.gov

phoid and hematopoietic neoplasms,[5] but some have been recognized more recently, and these have been covered in greater detail.

Monoclonal gammopathy of undetermined significance

Monoclonal gammopathy of undetermined significance (MGUS) is the archetype of an early lesion closely associ-

Table 1. Summary of key clinical, pathological, immunophenotypical and molecular features of early and indolent lymphoproliferative disorders.

Entity	Clinical/laboratory/pathological features	Immunophenotype: flow cytometry or immunohistochemistry	Molecular features
Monoclonal B-lymphocytosis (MBL)	CLL-like MBL: peripheral blood clonal B-cells 500-5000/μL Low-count MBL: peripheral blood clonal B-cells <100/μL	CLL-like: CD19$^+$, CD20dim, CD5$^+$, CD23$^+$, sIg dim Atypical CLL: CD5$^+$, CD20$^+$ bright, CD23$^{+/-}$ Non-CLL MBL: CD20$^+$,CD5$^-$, CD10$^-$	Clonal IG rearrangement
Monoclonal gammopathy of undetermined significance (MGUS)	Serum M-protein < 3 g/dL, Bone marrow monoclonal plasma cells <10%, No evidence of myeloma, lymphoproliferative disorder or amyloidosis	CD19$^-$, CD45$^{dim/-}$, CD56$^+$, CD20$^+$	Clonal IG rearrangement
Follicular lymphoma *in situ* Follicular lymphoma-like B cells of undetermined significance (FLIS/ FLBUS)	Incidental finding Lymph nodes have normal architecture Not diagnosed on routine microscopy	CD20$^+$, CD10$^+$, BCL6$^+$, BCL2$^+$	Clonal IG rearrangement t(14;18) (IGH-BCL2)
Mantle cell lymphoma *in situ* Mantle cell lymphoma-like cells of undetermined significance (MCLIS/MCLUS)	Incidental finding Lymph nodes have normal architecture Not diagnosed on routine microscopy	Inner mantle zone B cells: CD20$^+$, Cyclin D1$^+$, usually CD5-, Sox11-	Clonal IG rearrangement t(11;14) (IGH-CCND1)
Primary duodenal follicular lymphoma	Incidental finding Solitary or multiple polyps, mucosal nodularity or plaques in the small bowel Mainly duodenal, but can involve jejunum or ileum	CD20$^+$, CD10$^+$, BCL6$^+$, BCL2$^+$	Clonal IG rearrangement t(14;18) (IGH-BCL2) translocation present
Pediatric variant of follicular lymphoma	Males >> females; most often isolated cervical lymphadenopathy	CD20$^+$, CD10$^+$, BCL6$^+$, BCL2$^-$	Clonal IG rearrangement Absent t(14;18) (IGH-BCL2)
	Expansile, serpiginous follicles with a "starry sky" pattern, blastoid cells		
Pediatric nodal marginal zone lymphoma	Males >> females; most often isolated cervical lymphadenopathy Marginal zone expansion, fragmentation of germinal centers and PTGC-like changes	CD20$^+$, CD10$^-$, BCL6$^-$	Clonal IG rearrangement Trisomies 18, 3
Primary cutaneous follicle-center lymphoma	Solitary or grouped plaques, nodules in the head and neck or upper trunk. Non-epidermotropic infiltrate, composed predominantly of centrocytes.	CD20$^+$, BCL6$^+$, CD10$^{+/-}$, BCL2$^{-/+}$ (weak)	Clonal IG rearrangement Absent t(14;18) (IGH-BCL2)
Primary cutaneous marginal zone lymphoma	Solitary or multiple papules/nodules, most often upper extremities Non-epidermotropic infiltrate of small cells; plasmacytic component usually present	CD20$^+$, BCL6$^-$, CD10$^-$, BCL2$^+$ Plasma cells monotypic, usually IgG$^+$	Clonal IG rearrangement
Primary cutaneous small/medium CD4-positive T-cell lymphoma/LPD	Solitary head and neck nodules/papules Non-epidermotropic nodular lymphoid infiltrate of small/medium cells in the dermis and subcutis	CD3$^+$, CD4$^+$, PD-1$^+$, BCL6$^+$, usually CD10$^-$ B cells often abundant	Clonal TCR rearrangement
Indolent CD8+ T-cell lymphoproliferative disorder of the skin	Isolated nodules, skin of ear, and other acral sites Dense infiltrate of small, mature cells in the dermis	CD3$^+$, CD8$^+$, TIA1$^+$ but negative for Granzyme B	Clonal TCR rearrangement
Indolent T-cell lymphoproliferative disorder of the GI tract	Thickened mucosal folds and polyps on endoscopy. Dense infiltrate of small, mature cells in the lamina propria and submucosa. No epitheliotropism	CD3$^+$, CD8$^+$ > CD4$^+$ CD8 $^+$ cases are TIA1$^+$, but negative for Granzyme B	Clonal TCR rearrangement
Breast implant-associated anaplastic large cell lymphoma	Large cells with anaplastic morphology, hallmark cells seen in seroma fluid and implant capsule	CD3$^{+/-}$, CD30$^+$, ALK1-, cytotoxic markers +	Clonal TCR rearrangement
NK-cell enteropathy/ lymphomatoid gastropathy	Superficial ulcers or mucosal hemorrhages on endoscopy Dense infiltrate of atypical cells in lamina propria No epitheliotropism	CD3$^+$(cytoplasmic), CD7$^+$ CD56$^+$, CD2 +- Cytotoxic markers+, EBV-	Polyclonal TCR

PTGC: progressive transformation of germinal centers; LPD: lymphoproliferative disorder; GI: gastrointestinal; IG: immunoglobulin genes; TCR: T-cell receptor genes.

ated with its malignant counterpart, and nearly always precedes plasma cell myeloma.[6,7] The diagnostic criteria for MGUS are: serum M-protein less than 3 g/dL, BM monoclonal plasma cells less than 10%, no evidence of myeloma, lymphoproliferative disorders or amyloidosis.[8] The incidence of MGUS increases with age and has a small but definitive risk of progression to myeloma at an annual rate of 1%.[9] Multiple factors affect the progression of MGUS to myeloma.[10] IgM MGUS should be distinguished from MGUS associated with other heavy chain classes, and is closely tied to Waldenstrom's macroglobulinemia.[11]

MGUS and myeloma share cytogenetic alterations including major translocations involving the IGH gene; an increased incidence of chromosome 13 deletions is seen in myeloma in a background of specific cytogenetic aberrations suggesting a role in disease evolution.[12,13] Single nucleotide polymorphism (SNP) based-array studies have shown increasing copy number abnormalities during progression from MGUS to myeloma.[14] Recent studies have emphasized the significance of genetic alterations, suggesting that genetic profiling may prove to be an important tool in MGUS risk-stratification,[15] and support the view that progression of MGUS to myeloma results from the selection and expansion of multiple aberrant clones rather than a linear step-wise acquisition of specific genetic abnormalities.[16]

The current management of MGUS involves careful monitoring and no therapeutic intervention unless the patient is on a clinical trial.[17] The IMWG 2010 guidelines recommend MGUS risk-stratification based on the Mayo scheme. Low-risk MGUS patients should be followed up with serum electrophoresis six months after diagnosis and subsequently every 2-3 years, or when symptomatic. Intermediate-risk and high-risk MGUS patients should undergo a base-line bone marrow examination including cytogenetics and skeletal survey, and should be followed up with serum studies twice in the first year and annually thereafter.[18]

Monoclonal B-cell lymphocytosis

The widespread use of flow cytometric analysis has led to the detection of low levels of clonal B-cell populations with chronic lymphocytic leukemia (CLL)-like immunophenotype in asymptomatic individuals with normal peripheral blood counts.[19] MBL is defined as the presence of a circulating monoclonal B-cell population below 5 x 10^9/L, persisting for at least three months, in otherwise asymptomatic individuals.[20] Higher sensitivity flow cytometric analyses have shown an age-dependent increase in the prevalence of CLL-like B cells in individuals without lymphocytosis suggesting that the reported prevalence of MBL is dependent on diagnostic sensitivity.[21] Supporting this view, MBL has been diagnosed in normal healthy blood donors, over 45 years of age, at higher levels than previously reported.[22] Based on clonal B-cell counts and clinical significance, MBL is now subdivided into high-count MBL (0.5-5.0 x 10^9/L) and low-count MBL (< 0.1 x 10^9/L).[23]

High-count MBL has the highest prevalence amongst first-degree relatives of patients with CLL[21] and, unlike low-count MBL, has IGHV mutations with a repertoire similar to CLL suggesting a biological relationship.[24,25] However, both high-count and low-count MBL show CLL-related cytogenetic alterations including del13q, +12 and del17p, albeit at lower levels, suggesting that these

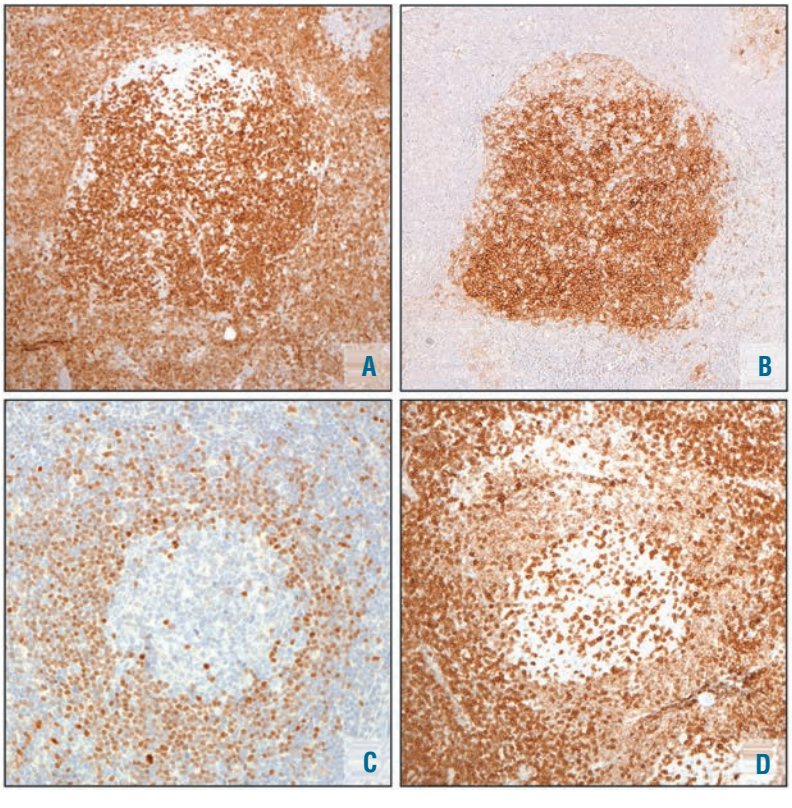

Figure 1. FLIS/FLBUS and MCL with a mantle zone pattern involving a single lymph node (A). A germinal center is largely replaced by strongly BCL2-positive centrocytes that also show high expression of CD10 (B). Other germinal centers in the same lymph node were negative for BCL2, but the mantle zone was replaced by B cells expressing cyclin D1 (C) and CD5 (D). Because the cyclin D1 positive cells extend focally beyond the mantle, the lesion does not fulfill criteria for MCLIS/MCLBUS.

changes occur early in clonal evolution and are not prognostically significant in the absence of B-cell lymphocytosis.[26]

High-count MBL progresses to CLL at an annual rate of 1-2% with the clonal B-cell count at presentation being the biggest risk factor. CD38 expression, IGHV mutation status and cytogenetic abnormalities were not significant risk factors on multivariate analysis,[24,27] although one study showed +12 or del17p as predictors of survival.[28]

The presence of palpable lymphadenopathy, organomegaly and/or bone marrow infiltration (> 30% of nucleated cells) fulfills the IWCLL criteria for CLL, even in the absence of clonal lymphocytosis[29] while the WHO criterion for CLL/SLL is the presence of any extramedullary involvement. However, a recent study suggested that limited nodal involvement, usually discovered incidentally, was still compatible with a diagnosis of MBL.[30] Risk factors for progression included lymphadenopathy greater than 1.5 cm by imaging and the presence of proliferation centers on histology. Bone marrow biopsies in patients with MBL have shown patchy interstitial lymphoid infiltrates indistinguishable from low-level involvement by CLL and a diagnosis of CLL should not be made on this evidence alone without supporting clinical information.[31] Further prospective studies are necessary to refine diagnostic criteria for tissue involvement with MBL.

Current recommendations for management of CLL-like MBL include yearly monitoring with intervention if clini-

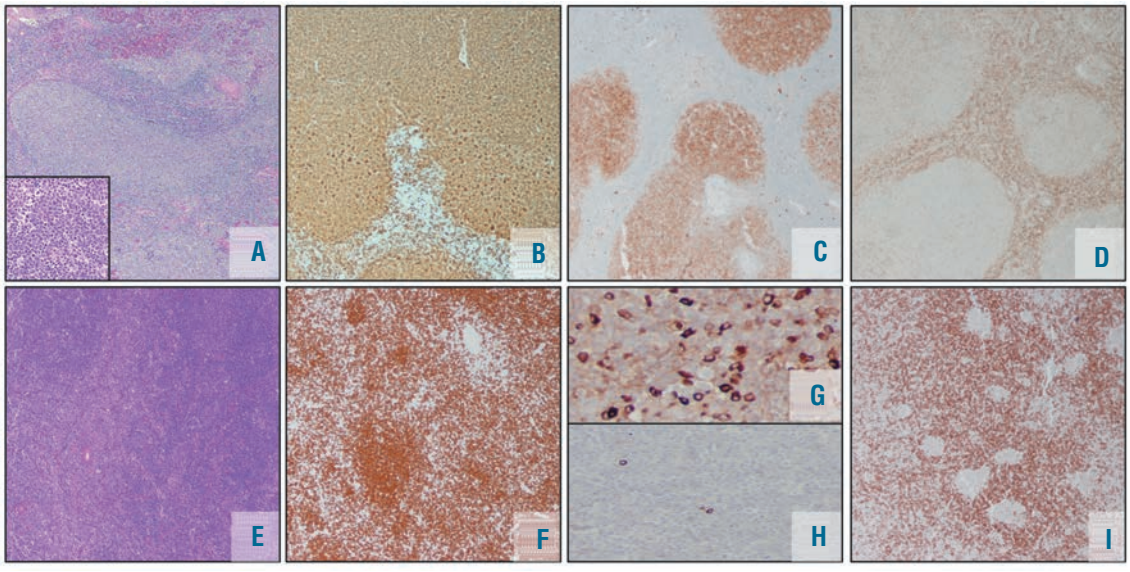

Figure 2. (A) Pediatric-type follicular lymphoma. Lymph node with large expansile follicles, with "starry sky" pattern and blastoid cells, positive for (B) CD20, (C) CD10, and negative for (D) BCL-2. (E) Pediatric marginal zone lymphoma. Fragmented follicles reminiscent of progressive transformation of germinal centers (PTGC) with interfollicular expansion by B cells, positive for (F) CD20 and (G) kappa-restricted (H, lambda). I, IgD demonstrates fragmentation of follicles.

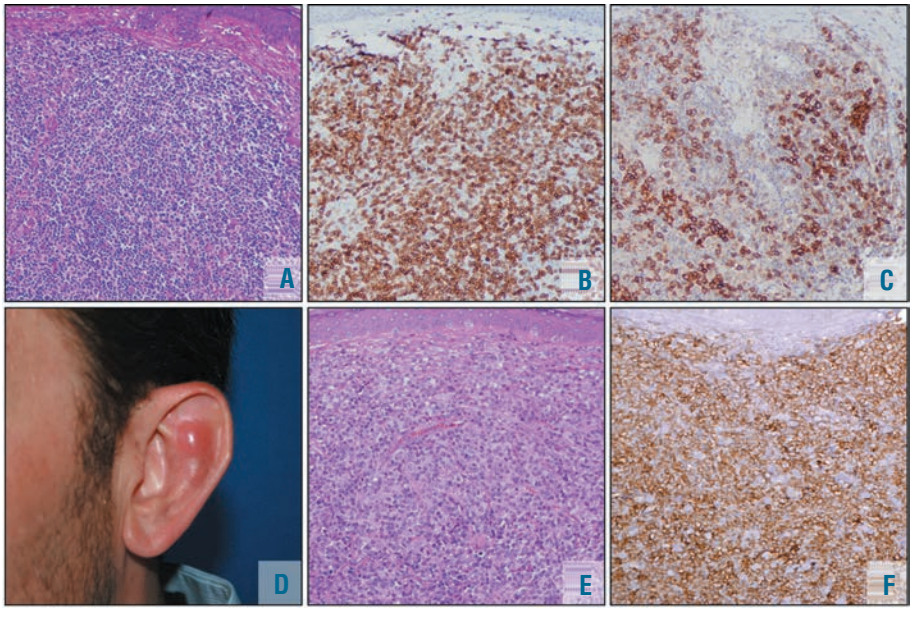

Figure 3. (A) Primary cutaneous small/medium CD4-positive T-cell lymphoma: dense non-epidermotropic dermal infiltrate of atypical cells positive for (B) CD3 and (C) PD-1. (D) Indolent CD8 lymphoid proliferation of the ear: solitary ear nodule composed of (E) dense non-epidermotropic dermal infiltrate of atypical cells positive for (F) CD8.

cally indicated. Low-count MBL, based on current data, is unlikely to progress to CLL and does not warrant clinical monitoring.[23] MBL with an atypical CLL-like phenotype (CD5+, bright CD20, CD23-) could represent an early leukemic manifestation of mantle cell lymphoma and a thorough staging workup including FISH testing for t(11;14) translocation is recommended. MBL with an atypical CLL- or non CLL-immunophenotype is rare and occurs in 1-2.5% of the general population.[32] These atypical clones can be transient and may be detected in patients with advanced HCV infection, possibly indicative of reactive clonal B-cell expansions.[33] Current guidelines recommend that patients with non-CLL-like MBL undergo a base-line evaluation to rule out a lymphoproliferative disorder, with follow up as clinically indicated.[21] However, a retrospective study of individuals with circulating B-cell clones consistent with a marginal zone phenotype (non-CLL-type MBL) showed a low rate of progression to lymphoma, indicating that these may also represent indolent proliferations not warranting aggressive intervention in the absence of symptoms.[34]

Follicular lymphoma in situ*/follicular lymphoma-like cells of undetermined significance*

Follicular lymphoma *in situ* (FLIS) was initially described as the localization of atypical B cells with strong expression of CD10 and BCL-2 in the germinal centers of reactive-appearing lymph nodes.[35] These cells have the t(14;18)(IgH-BCL2) translocation, seen in approximately 85% of overt low-grade follicular lymphoma (FL). Since the majority of patients with FLIS do not develop overt lymphoma and specific risk factors for disease progression are currently unknown, the alternate term "follicular lymphoma-like B-cells of undetermined significance" (FLBUS) was recently proposed.[1] Neither term is entirely satisfactory. "FLIS" might imply an expected risk for progression in most patients, not currently thought to be the case,[36] and "FLBUS" might lead to patient anxiety for a lesion now thought to have minimal, not undetermined, clinical significance, if other clinical evidence for lymphoma is lacking. The 4th edition of the WHO classification is currently under revision, and alternative terms will be considered. The incidence of FLIS/FLBUS in reactive lymphoid tissue is low (2-3%)[35,37] and only diagnosed with the aid of immunohistochemistry. The lymph node architecture is intact, with reactive appearing follicles, intact mantle zones and sharply defined germinal centers. The atypical cells resemble centrocytes and show molecular and immunophenotypic evidence of the BCL2 translocation. While one study found a correlation between the number of follicles involved by FLIS/FLBUS and the risk of subsequent lymphoma,[38] two other studies did not find the degree of involvement predictive of concurrent/subsequent lymphoma.[36,39]

FLIS/FLBUS must be differentiated from partial involvement by low-grade follicular lymphoma (PFL), which usually shows partially effaced nodal architecture with enlarged, crowded follicles and attenuated mantle zones.

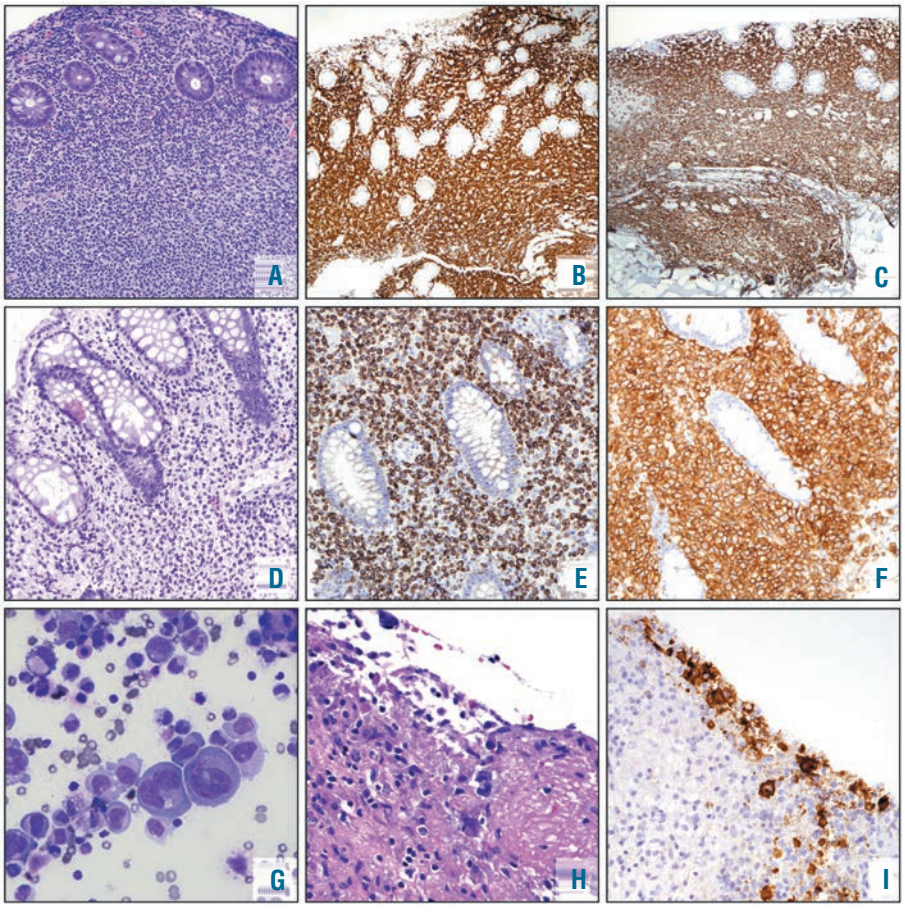

Figure 4. (A) Indolent CD8-lymphoproliferative of the GI tract: dense lamina propria infiltrate of small mature T cells positive for (B) CD3 and (C) CD8; (D) NK-cell enteropathy: dense superficial lamina propria infiltrate by small/medium cells with moderate pale cytoplasm positive for (E) CD3 and (F) CD56; (G) breast implant-associated anaplastic large cell lymphoma: effusion fluid containing large, atypical cells with irregular nuclei and abundant cytoplasm (H) Fibrous capsule with atypical large cells, including characteristic hallmark-cells positive for (I) CD30.

The atypical cells are a mixture of centrocytes and centroblasts, show variable intensity for CD10, BCL-2 and may extend beyond the germinal centers.[36] This distinction is clinically relevant as PFL is more likely to be associated with or progress to overt FL.

Low numbers of clonal B cells with the BCL2 translocation (follicular lymphoma-like B cells, FLLBC) may be detected in benign lymphoid tissue and peripheral blood of healthy subjects, a subject recently reviewed in detail by Mamessier *et al*.[40] FLLBC show preferential homing to the germinal centers of reactive lymph nodes and are non-proliferative.[41] Functionally, and in terms of risk, FLLBC in the blood of healthy individuals, and FLIS/FLBUS as detected histologically appear to be comparable. The higher incidence of circulating B cells with t(14;18) translocation in healthy subjects, compared to FLIS/FLBUS and the low rate of progression of FLIS/FLBUS, compared to PFL, to overt FL suggests these entities lie along a spectrum, and accumulate genetic alterations at every stage. Two recent high-resolution array CGH studies of FLIS/FLBUS identified a paucity of genetic aberrations in comparison with FL, supporting the conclusion that these lesions are at a very early stage of evolution, and do not represent merely seeding of germinal centers by lymphoma at a distant site.[42,43] Of note, evidence for EZH2 mutations, thought to occur early in follicular lymphomagenesis, were found in both reports. Duodenal follicular lymphoma (DFL) showed a similar low level of aberrations, while PFL appeared to represent an intermediate stage of evolution.[42]

The specific factors that determine progression of FLIS/FLBUS to FL still have to be clarified, but if there is no other evidence of disease at diagnosis, the risk of progression is low (less than 10%).[36] However, analogous to MGUS and MBL, retrospective review of "reactive" lymph nodes biopsied prior to a FL diagnosis has shown FLIS/FLBUS in a subset.[36,39] In approximately 15-20% of cases FLIS/FLBUS has been diagnosed in a lymph node involved by another B-cell lymphoma (Figure 1).[36,38,39] This finding might suggest that patients with FLIS/FLBUS are at increased risk, or it might be coincidental, due to the panel of immunostains routinely used to evaluate such biopsies.

Until more accurate predictive biomarkers are available, all patients with a diagnosis of FLIS/FLBUS should undergo a staging workup, including whole body imaging and bone marrow biopsy to rule out concurrent lymphoma. In the absence of overt lymphoma, conservative management is recommended, even in the presence of multi-focal FLIS/FLBUS and/or circulating FL-like cells identified by flow cytometry.[44] A recent study has shown that patients who developed FL had a higher number of circulating cells with the t(14;18) translocation compared with controls, identified up to 15 years preceding the diagnosis.[45] Thus, monitoring the level of FLLBC in the peripheral blood might provide useful information regarding the subsequent risk of FL.

Primary duodenal follicular lymphoma

Primary gastrointestinal (GI) follicular lymphoma is rare and most often involves the duodenum.[46-48] In view of its unique clinicopathological features, primary intestinal (duodenal) follicular lymphoma (DFL) was recognized as a separate variant of FL in the 2008 World Health Organization classification.[5] It shares many features with FLIS/FLBUS in terms of its usually benign natural history.

Most cases are diagnosed on endoscopy, often performed for reasons unrelated to the subsequent FL diagnosis. Endoscopic features include solitary or multiple polyps, mucosal nodularity or plaques. Multifocal involvement is typically seen, with lesions seen in the descending part of the duodenum, jejunum and rarely involving the ileum and limited to the mucosa/submucosa on imaging.[47] The risk of progression and dissemination is very low (<5%).[47]

Histologically, the atypical follicles are limited to the mucosa and submucosa, are well circumscribed, and composed almost entirely of centrocytes. The atypical B cells infiltrate the lamina propria and distort the villi. Molecular testing for *IGH* clonality or cytogenetics/ FISH analysis for t(14;18)(IGH-BCL2) is positive in the majority of cases.[47]

Studies have shown disrupted follicular dendritic cell (FDC) meshworks and lack of activation-induced deaminase (AID) expression in DFL, in contrast to nodal FL. The increased incidence of Ig VH4 and VH5 chains in DFL suggests an AID- and FDC-independent mechanism of somatic mutation,[49] and the expression of $\alpha 4\beta 7$ integrin, a mucosal homing integrin, and IgA, in DFL, supports a mucosal origin and local antigen-driven clonal expansion of B cells.[50]

High resolution array CGH analysis has shown that DFL shares genomic aberrations with FLIS and PFL suggesting common pathways of origin.[42] However, unlike in PFL, a large fraction of these alterations were not shared with FL. In the context of reduced AID expression in DFL, these aberrations could have occurred before downregulation of AID or independent of it. The lack of AID could also explain a reduced capacity for ongoing mutations and limited disease presentation.[40]

DFL has an indolent clinical course, with more than 95% of patients showing no systemic involvement or progression after a median follow up of 77 months. There were no significant differences in survival or time to progression between treated and untreated patients, supporting the view that in the absence of disease progression, judicious follow up and observation is preferred to aggressive therapy.[47] When treated, very high CR rates were obtained with either radiation or rituximab, or chemotherapy with or without radiation.[47] DFL should be distinguished from typical FL, which also can present with intestinal disease.[51] In such cases, mesenteric lymph node involvement is often present, and the mass may impinge on the lumen causing intestinal obstruction.

Mantle cell lymphoma in situ*/mantle cell lymphoma-like B cells of undetermined significance*

Analogous to FLIS/FLBUS, colonization of the mantle cuffs of reactive follicles by cyclin D1-positive B cells, diagnosed incidentally has been termed MCLIS or MCLBUS.[1,52] The positive cells carry the t(11;14)(*CCND1-IGH*) characteristic of mantle cell lymphoma (MCL). The same challenging issues of terminology that pertain to FLIS/FLBUS apply here as well.

MCLIS/MCLBUS is a rare incidental finding in lymph nodes or extranodal lymphoid tissue and is seen in a background of preserved architecture and reactive hyperplasia. The mantle zones are not expanded and the atypical cyclin D1-positive cells are seen predominantly within the inner layers of the mantle cuffs. These cases must be differentiated from early/partial involvement with overt

MCL with a mantle zone growth pattern (Figure 1C and D). This distinction is important as partial MCL is more likely to progress or co-exist with advanced disease.[52] Sox11 expression was present in less than 50% of MCLIS/MCLBUS cases in one study[52] while all MCLIS/MCLBUS cases submitted to a workshop were positive.[1] Whether Sox11 may be useful in predicting the risk of progression will require additional prospective studies.

MCLIS/MCLBUS is less common than FLIS in unselected lymph node biopsies,[53] and like FLIS/FLBUS, routine screening of lymphoid tissue for MCLIS/MCLBUS is not warranted. Interestingly, some cases have been detected retrospectively through examination of lymph nodes biopsied prior to a subsequent diagnosis of MCL, suggesting that, like in FLIS/FLBUS, the neoplastic clone may be present years earlier.[52] The *CCND1-IGH* translocation is likely an early event in mantle cell lymphomagenesis, supported by recent studies showing circulating B cells with this translocation in the peripheral blood of healthy subjects. Although MCL-like B cells are seen at a significantly lower frequency than FLLBC, these clones can also persist for several years.[54] Interestingly, MCLIS and FLIS have been detected concurrently in some cases,[55] possibly suggesting similar mechanisms of molecular pathogenesis.[56]

Current management recommendations for MCLIS/MCLBUS include whole body imaging and unilateral bone marrow biopsy (if indicated) to rule out a concomitant overt lymphoma. In the absence of overt disease, no treatment is required and careful follow up is advised.[44] The natural history of MCLIS/MCLBUS is unknown.

Pediatric variant of follicular lymphoma/pediatric-type follicular lymphoma

While usual FL is almost never seen in patients under 18 years of age, the WHO classification recognized a distinctive variant of FL mainly seen in the pediatric and young adult age group.[57,58] Known as the pediatric variant or pediatric type of FL (PTFL), it differs from the adult counterpart morphologically, immunophenotypically, and genetically.[59,60] It presents predominantly in young males, most often as isolated cervical lymphadenopathy. The tumor lacks the characteristic t(14;18)(IGH-BCL2) translocation, and is most often negative for BCL-2 protein as well. Lymph node architecture is partially or totally effaced by expansile, serpiginous follicles with a prominent "starry sky" appearance. The atypical follicles are composed of medium-sized to large blastoid cells, rather than typical centroblasts (Figure 2A-D).[57] However, grading as performed for usual FL is not required. The cells express BCL6 and CD10. However, BCL6 and MYC aberrations typically associated with aggressive B-cell lymphomas are absent.[57,58,61,62] Overlap with florid follicular hyperplasia remains a practical and theoretical problem, as most PTFL lack specific genetic aberrations, and whether some of these cases may represent limited clonal expansions in florid follicular hyperplasia is still a subject of debate.[63]

Nodal PTFL is an indolent disease with a very good prognosis. Most patients present with limited stage disease and have an excellent response to surgery alone or surgery followed by chemotherapy or radiotherapy.[57,58,61,64,65] Adverse risk factors of conventional FL, including high cytologic grade, absence of *BCL2* rearrangements, and high proliferative index, do not have an impact on prognosis in PTFL, suggesting that it is biologically and clinically distinct from conventional FL. While typically seen in young patients, cases with similar morphology and phenotype are also seen in adults.[57,58] Thus, the term "pediatric-type follicular lymphoma" was proposed to emphasize this behavior and ensure conservative management.[58]

Pediatric lymphomas with a follicular component that likely require more aggressive management include those with identifiable chromosomal aberrations.[62] Some of these will show association with diffuse large B-cell lymphoma. Another subset, often involving Waldeyer's ring, is associated with translocations involving *IRF4* and high expression of MUM1.[66] B-cell lymphomas with *IRF4* aberrations lack the distinctive features of the PTFL and are thought to represent a separate disease entity.[57]

Pediatric variant of nodal marginal zone lymphoma

Nodal marginal zone lymphoma, while uncommon in the pediatric population, shows characteristic clinical and pathological features. Similar to PTFL, pediatric NMZL is more common in males, especially in patients under 18 years of age, with a M:F ratio of 20:1.[67] It presents as asymptomatic isolated lymphadenopathy, commonly in the head and neck region. Morphologically, residual follicles are often present, and show fragmentation with thin mantle zones (Figure 2E-I). Clonality can usually be demonstrated by flow cytometry, immunohistochemistry or molecular analysis.[67,68] Approximately 20% of pediatric NMZL have cytogenetic aberrations. Trisomies of chromosomes 3 and 18 are the most common[68] and are also encountered in MZL in adults.[69]

Pediatric NMZL and PTFL show overlapping pathological features, in addition to marked clinical similarities.[57,58,67] These observations suggest a close relationship, and possibly a similar pathogenesis. Whether these are different faces of the same antigen driven process remains to be explored. Both should be distinguished from atypical marginal hyperplasia of the tonsils and appendix occurring in children with lambda light chain restriction, but negative for clonality by molecular studies.[70]

Pediatric NMZL is an indolent process with most patients presenting with localized, low-stage disease and no documented reports of large cell transformation. Surgical excision is curative in most patients with no reports of relapse.[67] Like PTFL, pediatric NMZL may be seen in adults.[71] Recognition of this unique, indolent variant can prevent misdiagnosis and overtreatment.

Primary cutaneous lymphomas of low malignant potential

The skin is the site of involvement of a group of primary cutaneous lymphomas or lymphoproliferative disorders that are clonal at the molecular level but have a very indolent clinical course, with a low risk of spread beyond the skin. They can be managed with local approaches in nearly all cases, and it could be questioned whether they properly belong among the group of "malignant lymphomas". They will briefly be reviewed as a group, given the common issues of clinical management.

Primary cutaneous follicle center lymphoma

Primary cutaneous follicle center lymphoma (PCFCL) comprises approximately 10% of all cutaneous lymphomas and is the most common cutaneous B-cell lymphoma. It was recognized as a separate entity in the 2008 WHO classification. It usually presents as solitary or

grouped plaques in the head and neck or trunk, sometimes with erythematous papules and nodules. Involvement of the extremities is rare. PCFCL can have a nodular, nodular and diffuse or entirely diffuse pattern involving the dermis and subcutaneous tissue. Centrocytes, which may be large, often predominate, and grading is not required. BCL2 expression, if positive, is weak and variable[72,73] but the t(14;18)(IGH-BCL2) translocation is usually negative, and if present, should raise concern for secondary cutaneous involvement.[74] Clonal immunoglobulin gene rearrangements can be detected in more than 90% of cases.[75,76] PCFCL has an excellent prognosis with more than 95% 5-year survival.[73,77] Small, well-demarcated solitary lesions are treated with surgical excision or radiation therapy with 40-70% of patients having cutaneous relapses.[78] Patients with few scattered lesions are treated with both radiotherapy of all visible skin lesions and a "wait-and-watch" approach. Patients with extensive skin lesions are treated with systemic rituximab (with a high rate of relapse in skin, although PFS is a median of 40 months) or combination chemoimmunotherapy considered in rare circumstances. Cutaneous relapses, occurring in nearly 30% of patients, do not signify a worse prognosis and a similar approach for management is recommended. In one study, PCFCL arising in the leg behaved more aggressively, suggesting the need for more aggressive therapy in this subset.[73] A biological basis for this observation has not been provided.

Primary cutaneous marginal zone lymphoma

Primary cutaneous marginal zone lymphoma (PCMZL) is considered a unique entity in the WHO-EORTC classification.[79] It is a rare B-cell neoplasm comprising less than 10% of all cutaneous lymphomas. *Borrelia burgdorferi* DNA has been identified in a minority of cases from endemic areas, suggesting a possible etiology, analogous to *H.pylori* infection and gastric MALT lymphomas.[80] However, other studies, including those from regions where *Borrelia* is common, have not confirmed this finding.[81,82]

PCMZL presents as solitary or multiple papules/nodules most often in the upper extremities, and is usually not seen in the head and neck. Plasmacytoid differentiation is common. However, in contrast to MZL in most other sites, the cells show evidence of class switching, and express IgG rather than IgM.[83] MALT-lymphoma associated translocations have not been described.[81,84,85] but clonality can usually be shown by PCR.[75,76]

PCMZL is an indolent disease with a 5-year disease-specific survival of over 95%.[77] Staging procedures with whole body imaging are recommended to rule out cutaneous involvement by MZL at other sites. Solitary lesions are excised with a "watch and wait" approach. Radiotherapy is effective for grouped lesions with intralesional steroids also being highly effective.[78] Cutaneous relapses are treated similarly and do not lead to a worse prognosis.

Primary cutaneous small/medium CD4-positive T-cell lymphoma

Primary cutaneous small/medium CD4-positive T-cell lymphoma (PCSMTCL) was a provisional entity in the WHO 2008 Classification. Clinically, these lesions are predominantly solitary, presenting in the head and neck area with rare lesions in the trunk and extremities. Histologically, nodular lymphoid infiltrates composed of small/medium cells with irregular, pleomorphic nuclei are seen in the dermis and subcutis without epidermotropism (Figure 3A-C).[86-88] The T cells have a follicular T-helper phenotype and a prominent interspersed B-cell population is seen.[87] Molecular analysis shows clonal T-cell receptor gene (TCRG) rearrangement in the majority of cases.[67,68]

The majority of PCSMTCL have shown an indolent clinical course. Systemic involvement has only been reported in one series, in a subset of patients with large tumors/nodules, which might represent a different disease.[89] Prognosis is generally favorable with long-term follow-up data from a subset of patients in the largest series reported showing no deaths or disseminated disease. Although therapy for PCSMTCL is not well defined, surgical excision or radiotherapy has resulted in durable remissions in patients with localized disease. We and others prefer the term "primary cutaneous small/medium CD4-positive lymphoproliferative disorder" instead of lymphoma, to prevent unnecessary aggressive therapy.[88]

Indolent CD8-positive lymphoid proliferation of the skin

Indolent CD8-positive lymphoid proliferation of the skin was described initially as a solitary nodule of the ear[90,91] but is now known to occur at other anatomic sites,[92] including the distal extremities.[93] Histology typically shows a non-epidermotropic, dense dermal lymphoid infiltrate composed of medium-sized atypical $CD8^+$ T cells positive for TIA-1, but negative for Granzyme B (Figure 3D-F). T-cell clonality has been demonstrated in most cases.[90,91] Initial evidence supports an indolent behavior with localized disease, and good response to surgery and radiotherapy. Rare patients have had persistent disease or local relapse but no deaths have been reported.[92]

This entity must be differentiated from primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma and primary cutaneous γδ T-cell lymphoma (PCGD-TCL). The latter entities present with localized or diffuse skin lesions with systemic dissemination and an aggressive clinical course.

Indolent T-cell lymphoproliferative disorders of the gastrointestinal tract

Primary T-cell lymphomas of the GI tract are rare and include enteropathy-associated T-cell lymphomas (EATL, type I and II), extranodal NK/T-cell lymphomas, nasal type and peripheral T-cell lymphomas, not otherwise specified (PTCL, NOS). All of these variants have an aggressive clinical course and poor prognosis. However, previously reported isolated case reports suggested that indolent GI T-cell lymphomas (Indolent T-LPD) might exist.[94-96]

Two recent studies have reported clonal T-cell proliferations of the GI tract with an indolent clinical course.[97,98] In both reports, the patients had GI symptoms suggesting either inflammatory bowel disease or celiac disease, but without response to a gluten free diet. Endoscopy revealed multiple sites of involvement, including oral cavity, esophagus, stomach, small bowel and colon. The lesions ranged from thickened mucosal folds, irregular appearing mucosa, friable erythematous mucosa or polyps. Imaging studies showed lesions limited to the GI tract.

Histologically, the lamina propria was expanded by a dense, non-destructive lymphoid infiltrate composed of small mature appearing lymphocytes. While mucosal glands were displaced by the infiltrate, epitheliotropism was not identified (Figure 4A-C). Small bowel villous blunting was not identified in the patients reported by

Perry *et al*.[98] whereas the presence of villous atrophy had suggested a diagnosis of celiac disease in the other report.[97] The infiltrating cells were αβ T cells in all cases studied, with a very low proliferative rate. Interestingly, there has not been a consistent phenotype, with both CD4- and CD8-expressing cases identified. However, molecular analysis showed a clonal TCRG rearrangement in all. STAT3 SH2 domain mutations, recently described in T-cell large granular lymphocytic leukemia and chronic NK-lymphoproliferative disorders,[99,100] were not identified in the 5 cases tested.[98]

Six out of the 10 cases reported by Perry *et al*. were initially diagnosed as PTCL and patients underwent chemotherapy, but with no improvement.[98] Four patients were observed without therapy. Most patients had persistent disease without progression or dissemination for up to 14 years. However, one case that was double-negative for CD4 and CD8 progressed with involvement of the liver (*AM Perry et al., 2013, personal communication*), and one case reported by Margolskee *et al*. underwent transformation to an intestinal large cell lymphoma with CD30 and cytotoxic marker expression.[97]

Correlation of clinical history, endoscopic findings, histological features and awareness of these indolent lesions are important to avoid misdiagnosis as PTCL and unwarranted aggressive therapy. Similarities with the indolent cutaneous T-cell LPD suggest the possibility of a response to an unknown antigen.

NK-cell enteropathy

NK-cell enteropathy is an indolent proliferation of NK-cells in the GI tract, also designated lymphomatoid gastropathy when limited to the stomach.[101-103] Patients are either asymptomatic or have non-specific GI symptoms and no history of celiac disease, inflammatory bowel disease or malabsorption.[102] A subset of patients in one study had a prior history of gastric carcinoma and frequent *H.pylori* infection.[103]

Endoscopic findings include superficial ulceration with surrounding hemorrhage and edema, with some patients showing multifocal involvement of the stomach, small bowel and colon. Luminal masses have not been described and imaging studies show no evidence of lymphadenopathy or organomegaly.[102,103]

The biopsies show expansion of the lamina propria by an atypical lymphoid infiltrate of intermediate cells with irregular nuclei, moderate pale to eosinophilic cytoplasm, seen in a mixed inflammatory background. Ulceration of the overlying mucosa is present but epitheliotropism as seen in EATL is not identified (Figure 4D-F). The atypical cells are positive for cytoplasmic CD3, CD7, CD56 and cytotoxic markers but negative for EBV. Molecular analysis for clonal TCRG is negative and cytogenetic studies have not been successful due to scant diagnostic material.[102,103]

The etiology of NK-cell enteropathy remains unknown. NK-cells are present in the GI tract as part of the innate immune system.[104] Native gut NK-cells produce cytokines but have poor cytotoxic activity, unless they are primed by exposure to antigens.[105] The atypical NK-cell infiltrates described above express cytotoxic markers, suggesting an activated phenotype. Nine out of 10 patients with lymphomatoid gastropathy were positive for *H.pylori*, but with a high prevalence of this infection in the Japanese population, and regression of lesions in some patients without antibiotic therapy, the significance of this finding is unknown.[103] Additional studies (cytogenetics, array CGH, mutation analyses) will help determine if these lesions are clonal expansions or an atypical reactive process.

NK-cell enteropathy/lymphomatoid gastropathy has a protracted but indolent clinical course with no involvement outside the GI tract or progression to an aggressive NK-cell neoplasm. The majority of cases reported in the literature had persistent lesions, some even after therapy, while a subset showed spontaneous regression. All patients were clinically stable and asymptomatic after a long follow up. Based on the indolent nature of this entity, observation without treatment is recommended.[102,103] Recognition of this unique entity and correlation with clinical features and endoscopic findings is critical to prevent a misdiagnosis of lymphoma.

Breast implant-associated anaplastic large-cell lymphoma

Non-Hodgkin lymphomas involving the breast are predominantly of B-cell type while T-cell lymphomas are rare. However, ALCL, ALK-negative associated with breast implants were first reported in 1997.[106] In 2011, the US Food and Drug Administration reported 60 documented cases of breast implant-associated ALCL. The real incidence of this entity may be higher, as seroma effusions have been inconsistently submitted for microscopic examination.[107]

In a recent review, no statistical difference was identified between indication for breast-implants (cosmetic *vs.* reconstructive surgery), laterality and type of implant (saline *vs.* silicone).[108] The median time to diagnosis of ALCL after implantation was nine years. Patients most often presented with a peri-implant effusion (seroma) or less commonly with a mass adjacent to the effusion. The majority of the patients underwent explantation, drainage of the effusion and capsular excision. Tumor cells were seen in the effusion fluid and capsule, without extra-capsular extension (cases with effusion) or forming distinct aggregates outside the capsule (cases with tumor mass). The cells had anaplastic morphology, including distinctive hallmark cells, and were strongly CD30-positive and ALK-negative (Figure 4G-I). Molecular analysis showed clonal TCRG rearrangements in 28 of 29 cases tested.[108]

Clinical management was variable and ranged from capsulectomy, mastectomy, radiotherapy, chemotherapy and autologous stem cell transplantation. While median follow-up periods are short (2 years), 93% of patients without a mass had a complete remission compared to 72% of patients with a mass. Interestingly, adjuvant chemotherapy did not significantly improve clinical outcome and remission rates were much better than systemic ALK-negative ALCL.[108] If there is no capsular invasion, conservative management with implant and capsular removal is favored.

Conclusions

In this review we have discussed a group of lymphoproliferative disorders that have unique features and are associated with an indolent behavior. They can be broadly divided into two groups. The first group includes MGUS, MBL, FLIS/FLBUS and MCLIS/MCLBUS. These are clonal

proliferations that share genetic and molecular alterations with well-characterized lymphoid neoplasms, multiple myeloma, CLL/SLL, follicular lymphoma and mantle cell lymphoma. However, these "early forms" are often diagnosed incidentally with only a small fraction progressing to symptomatic disease. Studying these precursor lesions has provided insight into the biology of lymphomagenesis in a manner analogous to the "adenoma-carcinoma" pathways in epithelial malignancies. The use of highly sensitive ancillary and screening tests has led to an increase in the diagnosis of these entities and the emphasis over the past few years has been to identify factors that may play a role in progression, to better assess patient risk, and provide a rationale for patient management. A second group of clonal lymphoid proliferations resemble lymphoma, but are associated with an indolent clinical course and excellent prognosis. They appear to lack the molecular alterations leading to autonomous growth and clinically malignant behavior. However, due to the clonal nature of the proliferation, and the sometimes atypical clinical or pathological features, they have been diagnosed as "lymphomas". They may represent an exaggerated response to antigen, clonal but self-limited. This scenario seems most likely for the pediatric variants of nodal FL and MZL. For some conditions, such as breast-implant associated ALCL, the benign clinical behavior may be related to the anatomically confined nature of the proliferation within the capsule surrounding the implant. If the cells escape this compartment, the risk for progression is much greater. Further studies are required to understand the molecular aberrations that lead to autonomous growth. Integration of clinical and pathological data and awareness of these entities is crucial to prevent misdiagnosis and subsequent inappropriate therapy.

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References

1. Fend F, Cabecadas J, Gaulard P, Jaffe ES, Kluin P, Kuzu I, et al. Early lesions in lymphoid neoplasia: Conclusions based on the Workshop of the XV. Meeting of the European Association of Hematopathology and the Society of Hematopathology, in Uppsala, Sweden. J Hematop. 2012;5:169-99.
2. Janz S, Potter M, Rabkin CS. Lymphoma- and leukemia-associated chromosomal translocations in healthy individuals. Genes Chromosomes Cancer. 2003;36(3):211-23.
3. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood. 2011;118(15):4024-35.
4. Pittaluga S. Viral-associated lymphoid proliferations. Semin Diagn Pathol. 2013;30(2):130-6.
5. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. 2008.
6. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009;113(22):5412-7.
7. Weiss BM, Abadie J, Verma P, Howard RS, Kuehl WM. A monoclonal gammopathy precedes multiple myeloma in most patients. Blood. 2009;113(22):5418-22.
8. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol. 2003;121(5):749-57.
9. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med. 2002;346(8):564-9.
10. Mailankody S, Mena E, Yuan CM, Balakumaran A, Kuehl WM, Landgren O. Molecular and biologic markers of progression in monoclonal gammopathy of undetermined significance to multiple myeloma. Leuk Lymphoma. 2010;51(12):2159-70.
11. Kristinsson SY, Bjorkholm M, Landgren O. Survival in monoclonal gammopathy of undetermined significance and Waldenstrom macroglobulinemia. Clin Lymphoma Myeloma Leuk. 2013;13(2):187-90.
12. Chiecchio L, Dagrada GP, Protheroe RK, Stockley DM, Smith AG, Orchard KH, et al. Loss of 1p and rearrangement of MYC are associated with progression of smouldering myeloma to myeloma: sequential analysis of a single case. Haematologica. 2009;94:(7)1024-8.
13. Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its premalignant precursor. J Clin Invest. 2012;122(10):3456-63.
14. López-Corral L, Sarasquete ME, Beà S, García-Sanz R, Mateos MV, Corchete LA, et al. SNP-based mapping arrays reveal high genomic complexity in monoclonal gammopathies, from MGUS to myeloma status. Leukemia. 2012;26(12):2521-9.
15. Dhodapkar MV, Sexton R, Waheed S, Usmani S, Papanikolaou X, Nair B, et al. Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). Blood. 2014;123(1):78-85.
16. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. Nat Rev Cancer. 2012;12(5):335-48.
17. Landgren O. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: biological insights and early treatment strategies. Hematology Am Soc Hematol Educ Program. 2013;2013:478-87.
18. Kyle RA, Durie BG, Rajkumar SV, Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia. 2010;24(6):1121-7.
19. Rawstron AC, Green MJ, Kuzmicki A, Kennedy B, Fenton JAL, Evans PAS, et al. Monoclonal B lymphocytes with the characteristics of "indolent" chronic lymphocytic leukemia are present in 3.5% of adults with normal blood counts. Blood. 2002;100(2):635-9.
20. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.
21. Shanafelt TD, Ghia P, Lanasa MC, Landgren O, Rawstron AC. Monoclonal B-cell lymphocytosis (MBL): biology, natural history and clinical management. Leukemia 2010;24(3):512-20.
22. Shim YK, Rachel JM, Ghia P, Boren J, Abbasi F, Dagklis A, et al. Monoclonal B-cell lymphocytosis in healthy blood donors: an unexpectedly common finding. Blood. 2014;123(9):1319-26.
23. Rawstron AC. Monoclonal B cell lymphocytosis--what does it really mean? Curr Hematol Malig Rep. 2013;8:52-9.
24. Rawstron AC, Bennett FL, O'Connor SJM, Kwok M, Fenton JAL, Plummer M, et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. N Engl J Med. 2008;359:575-83.
25. Dagklis A, Fazi C, Sala C, Cantarelli V, Scielzo C, Massacane R, et al. The immunoglobulin gene repertoire of low-count chronic lymphocytic leukemia (CLL)-like monoclonal B lymphocytosis is different from CLL: diagnostic implications for clinical monitoring. Blood. 2009;114(1):26-32.
26. Fazi C, Scarfò L, Pecciarini L, Cottini F, Dagklis A, Janus A, et al. General population low-count CLL-like MBL persists over time without clinical progression, although carrying the same cytogenetic abnormalities of CLL. Blood. 2011;118(25):6618-25.
27. Shanafelt TD, Kay NE, Rabe KG, Call TG, Zent CS, Maddocks K, et al. Brief report:

natural history of individuals with clinically recognized monoclonal B-cell lymphocytosis compared with patients with Rai 0 chronic lymphocytic leukemia. J Clin Oncol. 2009;27(24):3959-63.
28. Rossi D, Sozzi E, Puma A, De Paoli L, Rasi S, Spina V, et al. The prognosis of clinical monoclonal B cell lymphocytosis differs from prognosis of Rai 0 chronic lymphocytic leukaemia and is recapitulated by biological risk factors. Br J Haematol. 2009;146(1):64-75.
29. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111 (12):5446-56.
30. Gibson SE, Swerdlow SH, Ferry JA, Surti U, Dal Cin P, Harris NL, et al. Reassessment of small lymphocytic lymphoma in the era of monoclonal B-cell lymphocytosis. Haematologica. 2011;96(8):1144-52.
31. Randen U, Tierens AM, Tjonnfjord GE, Delabie J. Bone marrow histology in monoclonal B-cell lymphocytosis shows various B-cell infiltration patterns. Am J Clin Pathol. 2013;139(3):390-5.
32. Ghia P, Prato G, Scielzo C, Stella S, Geuna M, Guida G, et al. Monoclonal CD5+ and CD5- B-lymphocyte expansions are frequent in the peripheral blood of the elderly. Blood. 2004;103(6):2337-42.
33. Fazi C, Dagklis A, Cottini F, Scarfò L, Bertilaccio MTS, Finazzi R, et al. Monoclonal B cell lymphocytosis in hepatitis C virus infected individuals. Cytometry B Clin Cytom. 2010;78 Suppl 1:S61-8.
34. Xochelli A, Kalpadakis C, Gardiner A, Baliakas P, Vassilakopoulos TP, Mould S, et al. Clonal B-cell lymphocytosis exhibiting immunophenotypic features consistent with a marginal zone origin: is this a distinct entity? Blood. 2014; 123(8):11999-206.
35. Cong P, Raffeld M, Teruya-Feldstein J, Sorbara L, Pittaluga S, Jaffe ES. In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. Blood. 2002;99(9):3376-82.
36. Jegalian AG, Eberle FC, Pack SD, Mirvis M, Raffeld M, Pittaluga S, et al. Follicular lymphoma in situ: clinical implications and comparisons with partial involvement by follicular lymphoma. Blood. 2011;118(11):2976-84.
37. Henopp T, Quintanilla-Martínez L, Fend F, Adam P. Prevalence of follicular lymphoma in situ in consecutively analysed reactive lymph nodes. Histopathology. 2011;59(1):139-42.
38. Montes-Moreno S, Castro Y, Rodríguez-Pinilla SM, García JF, Mollejo M, Castillo ME, et al. Intrafollicular neoplasia/in situ follicular lymphoma: review of a series of 13 cases. Histopathology. 2010;56(5):658-62.
39. Pillai RK, Surti U, Swerdlow SH. Follicular lymphoma-like B cells of uncertain significance (in situ follicular lymphoma) may infrequently progress, but precedes follicular lymphoma, is associated with other overt lymphomas and mimics follicular lymphoma in flow cytometric studies. Haematologica. 2013;98(10):1571-80.
40. Mamessier E, Broussais-Guillaumot F, Chetaille B, Bouabdallah R, Xerri L, Jaffe ES, et al. Nature and importance of follicular lymphoma precursors. Haematologica. 2014;99(5):802-10.
41. Tellier J, Menard C, Roulland S, Martin N, Monvoisin C, Chasson L, et al. Human t(14;18)positive germinal center B cells: a new step in follicular lymphoma pathogenesis? Blood. 2014;22(22):3462-5.
42. Mamessier E, Song JY, Eberle FC, Pack S, Drevet C, Chetaille B, et al. Early lesions of follicular lymphoma: a genetic perspective. Haematologica. 2014;99(3):481-8.
43. Schmidt J, Salaverria I, Haake A, Bonzheim I, Adam P, Montes-Moreno S, et al. Increasing genomic and epigenomic complexity in the clonal evolution from in situ to manifest t(14;18)-positive follicular lymphoma. Leukemia. 2014;28(5):1103-12.
44. Carbone A, Santoro A. How I treat: diagnosing and managing "in situ" lymphoma. Blood. 2011;117(15):3954-60.
45. Roulland S, Kelly RS, Morgado E, Sungalee S, Solal-Celigny P, Colombat P, et al. t(14;18) Translocation: A Predictive Blood Biomarker for Follicular Lymphoma. J Clin Oncol. 2014;32(13):1347-55.
46. Yoshino T, Miyake K, Ichimura K, Mannami T, Ohara N, Hamazaki S, et al. Increased incidence of follicular lymphoma in the duodenum. Am J Surg Pathol. 2000; 24(5):688-93.
47. Schmatz A-I, Streubel B, Kretschmer-Chott E, Püspök A, Jäger U, Mannhalter C, et al. Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma: a retrospective study of 63 cases. J Clin Oncol. 2011; 29(11):1445-51.
48. Yamamoto S, Nakase H, Yamashita K, Matsuura M, Takada M, Kawanami C, et al. Gastrointestinal follicular lymphoma: review of the literature. J Gastroenterol 2010;45(4):370-88.
49. Takata K, Sato Y, Nakamura N, Kikuti YY, Ichimura K, Tanaka T, et al. Duodenal and nodal follicular lymphomas are distinct: the former lacks activation-induced cytidine deaminase and follicular dendritic cells despite ongoing somatic hypermutations. Mod Pathol. 2009;22(7):940-9.
50. Bende RJ, Smit LA, Bossenbroek JG, Aarts WM, Spaargaren M, de Leval L, et al. Primary follicular lymphoma of the small intestine: alpha4beta7 expression and immunoglobulin configuration suggest an origin from local antigen-experienced B cells. Am J Pathol. 2003;162(1):105-13.
51. Misdraji J, Harris NL, Hasserjian RP, Lauwers GY, Ferry JA. Primary follicular lymphoma of the gastrointestinal tract. Am J Surg Pathol. 2011;35(9):1255-63.
52. Carvajal-Cuenca A, Sua LF, Silva NM, Pittaluga S, Royo C, Song JY, et al. In situ mantle cell lymphoma: clinical implications of an incidental finding with indolent clinical behavior. Haematologica. 2012;97(2):270-8.
53. Adam P, Schiefer A-I, Prill S, Henopp T, Quintanilla-Martínez L, Bösmüller H-C, et al. Incidence of preclinical manifestations of mantle cell lymphoma and mantle cell lymphoma in situ in reactive lymphoid tissues. Mod Pathol. 2012;25(12):1629-36.
54. Lecluse Y, Lebailly P, Roulland S, Gac AC, Nadel B, Gauduchon P. t(11;14)-positive clones can persist over a long period of time in the peripheral blood of healthy individuals. Leukemia. 2009;23(6):1190-3.
55. Roullet MR, Martinez D, Ma L, Fowler MH, McPhail ED, Judkins A, et al. Coexisting follicular and mantle cell lymphoma with each having an in situ component: A novel, curious, and complex consultation case of coincidental, composite, colonizing lymphoma. Am J Clin Pathol. 2010;133(4):584-91.
56. Greisman HA, Lu Z, Tsai AG, Greiner TC, Yi HS, Lieber MR. IgH partner breakpoint sequences provide evidence that AID initiates t(11;14) and t(8;14) chromosomal breaks in mantle cell and Burkitt lymphomas. Blood. 2012;120(14):2864-7.
57. Liu Q, Salaverria I, Pittaluga S, Jegalian AG, Xi L, Siebert R, et al. Follicular lymphomas in children and young adults: a comparison of the pediatric variant with usual follicular lymphoma. Am J Surg Pathol. 2013; 37(3):333-43.
58. Louissaint A Jr, Ackerman AM, Dias-Santagata D, Ferry JA, Hochberg EP, Huang MS, et al. Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement. Blood. 2012;120(12):2395-404.
59. Frizzera G, Murphy SB. Follicular (nodular) lymphoma in childhood: a rare clinical-pathological entity. Report of eight cases from four cancer centers. Cancer. 1979;44 (6):2218-35.
60. Pinto A, Hutchison RE, Grant LH, Trevenen CL, Berard CW. Follicular lymphomas in pediatric patients. Mod Pathol. 1990;3:308-13.
61. Oschlies I, Salaverria I, Mahn F, Meinhardt A, Zimmermann M, Woessmann W, et al. Pediatric follicular lymphoma--a clinicopathological study of a population-based series of patients treated within the Non-Hodgkin's Lymphoma--Berlin-Frankfurt-Munster (NHL-BFM) multicenter trials. Haematologica. 2010;95(2):253-9.
62. Martin-Guerrero I, Salaverria I, Burkhardt B, Szczepanowski M, Baudis M, Bens S, et al. Recurrent loss of heterozygosity in 1p36 associated with TNFRSF14 mutations in IRF4 translocation negative pediatric follicular lymphomas. Haematologica. 2013;98(8): 1237-41.
63. Kussick SJ, Kalnoski M, Braziel RM, Wood BL. Prominent Clonal B-Cell Populations Identified by Flow Cytometry in Histologically Reactive Lymphoid Proliferations. Am J Clin Pathol. 2004;121 (4):464-72.
64. Atra A, Meller ST, Stevens RS, Hobson R, Grundy R, Carter RL, et al. Conservative management of follicular non-Hodgkin's lymphoma in childhood. Br J Haematol. 1998;103(1):220-3.
65. Lorsbach RB, Shay-Seymore D, Moore J, Banks PM, Hasserjian RP, Sandlund JT, et al. Clinicopathologic analysis of follicular lymphoma occurring in children. Blood. 2002;99(6):1959-64.
66. Salaverria I, Philipp C, Oschlies I, Kohler CW, Kreuz M, Szczepanowski M, et al. Translocations activating IRF4 identify a subtype of germinal center-derived B-cell lymphoma affecting predominantly children and young adults. Blood. 2011;118(1):139-47.
67. Taddesse-Heath L, Pittaluga S, Sorbara L, Bussey M, Raffeld M, Jaffe ES. Marginal zone B-cell lymphoma in children and young adults. Am J Surg Pathol. 2003;27 (4):522-31.
68. Rizzo KA, Streubel B, Pittaluga S, Chott A, Xi L, Raffeld M, et al. Marginal zone lymphomas in children and the young adult population; characterization of genetic aberrations by FISH and RT-PCR. Mod Pathol. 2010;23(6):866-73.
69. Dierlamm J, Pittaluga S, Wlodarska I, Stul M, Thomas J, Boogaerts M, et al. Marginal zone B-cell lymphomas of different sites share similar cytogenetic and morphologic features. Blood. 1996;87(1):299-307.

70. Attygalle AD, Liu H, Shirali S, Diss TC, Loddenkemper C, Stein H, et al. Atypical marginal zone hyperplasia of mucosa-associated lymphoid tissue: a reactive condition of childhood showing immunoglobulin lambda light-chain restriction. Blood. 2004;104(10):3343-8.
71. Gitelson E, Al-Saleem T, Robu V, Millenson MM, Smith MR. Pediatric nodal marginal zone lymphoma may develop in the adult population. Leuk Lymphoma. 2010;51(1): 89-94.
72. Kim BK, Surti U, Pandya A, Cohen J, Rabkin MS, Swerdlow SH. Clinicopathologic, immunophenotypic, and molecular cytogenetic fluorescence in situ hybridization analysis of primary and secondary cutaneous follicular lymphomas. Am J Surg Pathol. 2005;29(1):69-82.
73. Senff NJ, Hoefnagel JJ, Jansen PM, Vermeer MH, van Baarlen J, Blokx WA, et al. Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. J Clin Oncol. 2007;25(12):1581-7.
74. Swerdlow SH, Quintanilla-Martinez L, Willemze R, Kinney MC. Cutaneous B-cell lymphoproliferative disorders: report of the 2011 Society for Hematopathology/ European Association for Haematopathology workshop. Am J Clin Pathol. 2013;139(4):515-35.
75. Morales AV, Advani R, Horwitz SM, Riaz N, Reddy S, Hoppe RT, et al. Indolent primary cutaneous B-cell lymphoma: experience using systemic rituximab. J Am Acad Dermatol. 2008;59(6):953-7.
76. Felcht M, Booken N, Stroebel P, Goerdt S, Klemke CD. The value of molecular diagnostics in primary cutaneous B-cell lymphomas in the context of clinical findings, histology, and immunohistochemistry. J Am Acad Dermatol. 2011;64(1):135-43.
77. Hallermann C, Niermann C, Fischer RJ, Schulze HJ. Survival data for 299 patients with primary cutaneous lymphomas: a monocentre study. Acta Derm Venereol. 2011;91(5):521-5.
78. Senff NJ, Noordijk EM, Kim YH, Bagot M, Berti E, Cerroni L, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood. 2008;112(5):1600-9.
79. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768-85.
80. Cerroni L, Zochling N, Putz B, Kerl H. Infection by Borrelia burgdorferi and cutaneous B-cell lymphoma. J Cutan Pathol. 1997;24:457-61.
81. Takino H, Li C, Hu S, Kuo TT, Geissinger E, Muller-Hermelink HK, et al. Primary cutaneous marginal zone B-cell lymphoma: a molecular and clinicopathological study of cases from Asia, Germany, and the United States. Mod Pathol. 2008;21(12):1517-26.
82. Ponzoni M, Ferreri AJ, Mappa S, Pasini E, Govi S, Facchetti F, et al. Prevalence of Borrelia burgdorferi infection in a series of 98 primary cutaneous lymphomas. Oncologist. 2011;16(11):1582-8.
83. Edinger JT, Kant JA, Swerdlow SH. Cutaneous marginal zone lymphomas have distinctive features and include 2 subsets. Am J Surg Pathol. 2010;34(12):1830-41.
84. Hallermann C, Kaune KM, Gesk S, Martin-Subero JI, Gunawan B, Griesinger F, et al. Molecular cytogenetic analysis of chromosomal breakpoints in the IGH, MYC, BCL6, and MALT1 gene loci in primary cutaneous B-cell lymphomas. J Invest Dermatol. 2004;123(1):213-9.
85. Wongchaowart NT, Kim B, Hsi ED, Swerdlow SH, Tubbs RR, Cook JR. t(14;18)(q32;q21) involving IGH and MALT1 is uncommon in cutaneous MALT lymphomas and primary cutaneous diffuse large B-cell lymphomas. J Cutan Pathol. 2006;33(4):286-92.
86. Grogg KL, Jung S, Erickson LA, McClure RF, Dogan A. Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma: a clonal T-cell lymphoproliferative disorder with indolent behavior. Mod Pathol. 2008;21(6):708-15.
87. Rodriguez Pinilla SM, Roncador G, Rodriguez-Peralto JL, Mollejo M, Garcia JF, Montes-Moreno S, et al. Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma expresses follicular T-cell markers. Am J Surg Pathol. 2009;33(1):81-90.
88. Beltraminelli H, Leinweber B, Kerl H, Cerroni L. Primary cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphoma: a cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance? A study of 136 cases. Am J Dermatopathol. 2009;31(4):317-22.
89. Garcia-Herrera A, Colomo L, Camos M, Carreras J, Balague O, Martinez A, et al. Primary cutaneous small/medium CD4+ T-cell lymphomas: a heterogeneous group of tumors with different clinicopathologic features and outcome. J Clin Oncol. 2008;26 (20):3364-71.
90. Petrella T, Maubec E, Cornillet-Lefebvre P, Willemze R, Pluot M, Durlach A, et al. Indolent CD8-positive lymphoid proliferation of the ear: a distinct primary cutaneous T-cell lymphoma? Am J Surg Pathol. 2007;31(12):1887-92.
91. Beltraminelli H, Mullegger R, Cerroni L. Indolent CD8+ lymphoid proliferation of the ear: a phenotypic variant of the small-medium pleomorphic cutaneous T-cell lymphoma? J Cutan Pathol. 2010;37(1):81-4.
92. Greenblatt D, Ally M, Child F, Scarisbrick J, Whittaker S, Morris S, et al. Indolent CD8(+) lymphoid proliferation of acral sites: a clinicopathologic study of six patients with some atypical features. J Cutan Pathol. 2013;40(2):248-58.
93. Wobser M, Petrella T, Kneitz H, Kerstan A, Goebeler M, Rosenwald A, et al. Extrafacial indolent CD8-positive cutaneous lymphoid proliferation with unusual symmetrical presentation involving both feet. J Cutan Pathol. 2013;40(11):955-61.
94. Egawa N, Fukayama M, Kawaguchi K, Hishima T, Hayashi Y, Funata N, et al. Relapsing oral and colonic ulcers with monoclonal T-cell infiltration. A low grade mucosal T-lymphoproliferative disease of the digestive tract. Cancer. 1995;75(7):1728-33.
95. Carbonnel F, d'Almagne H, Lavergne A, Matuchansky C, Brouet JC, Sigaux F, et al. The clinicopathological features of extensive small intestinal CD4 T cell infiltration. Gut. 1999;45(5):662-7.
96. Ranheim EA, Jones C, Zehnder JL, Warnke R, Yuen A. Spontaneously relapsing clonal, mucosal cytotoxic T-cell lymphoproliferative disorder: case report and review of the literature. Am J Surg Pathol. 2000;24(2): 296-301.
97. Margolskee E, Jobanputra V, Lewis SK, Alobeid B, Green PH, Bhagat G. Indolent small intestinal CD4+ T-cell lymphoma is a distinct entity with unique biologic and clinical features. PLoS One. 2013;8(7):e68343.
98. Perry AM, Warnke RA, Hu Q, Gaulard P, Copie-Bergman C, Alkan S, et al. Indolent T-cell lymphoproliferative disease of the gastrointestinal tract. Blood. 2013;122 (22):3599-606.
99. Jerez A, Clemente MJ, Makishima H, Koskela H, Leblanc F, Peng Ng K, et al. STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. Blood. 2012;120(15):3048-57.
100. Koskela HLM, Eldfors S, Ellonen P, van Adrichem AJ, Kuusanmäki H, Andersson EI, et al. Somatic STAT3 mutations in large granular lymphocytic leukemia. N Engl J Med. 2012;366(20):1905-13.
101. Vega F, Chang CC, Schwartz MR, Preti HA, Younes M, Ewton A, et al. Atypical NK-cell proliferation of the gastrointestinal tract in a patient with antigliadin antibodies but not celiac disease. Am J Surg Pathol. 2006;30(4): 539-44.
102. Mansoor A, Pittaluga S, Beck PL, Wilson WH, Ferry JA, Jaffe ES. NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series. Blood. 2011;117(5):1447-52.
103. Takeuchi K, Yokoyama M, Ishizawa S, Terui Y, Nomura K, Marutsuka K, et al. Lymphomatoid gastropathy: a distinct clinicopathologic entity of self-limited pseudomalignant NK-cell proliferation. Blood. 2010;116(25):5631-7.
104. Bjorkstrom NK, Kekalainen E, Mjosberg J. Tissue-specific effector functions of innate lymphoid cells. Immunology. 2013;139(4): 416-27.
105. Chinen H, Matsuoka K, Sato T, Kamada N, Okamoto S, Hisamatsu T, et al. Lamina propria c-kit+ immune precursors reside in human adult intestine and differentiate into natural killer cells. Gastroenterology. 2007; 133(2):559-73.
106. Keech JA Jr, Creech BJ. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. Plast Reconstr Surg. 1997; 100(2):554-5.
107. Zarbo RJ, Nakhleh RE. Surgical pathology specimens for gross examination only and exempt from submission: a College of American Pathologists Q-Probes study of current policies in 413 institutions. Arch Pathol Lab Med. 1999;123(2):133-9.
108. Miranda RN, Aladily TN, Prince HM, Kanagal-Shamanna R, de Jong D, Fayad LE, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol. 2014;32(2):114-20.