Received: 24 May 2020 | Revised: 4 August 2020 | Accepted: 17 August 2020

DOI: 10.1111/cup.13858

REVIEW

JOURNAL OF CUTANEOUS PATHOLOGY WILEY

Kappa and lambda immunohistochemistry and in situ hybridization in the evaluation of atypical cutaneous lymphoid infiltrates

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Abstract

Background: Atypical cutaneous lymphoid infiltrates are challenging lesions in dermatopathology. We present a summary of the literature regarding kappa and lambda immunohistochemistry (IHC) and in situ hybridization (ISH) in the evaluation of atypical cutaneous or mucosal lymphoid infiltrates.

Methods: Relevant articles from 1967 to 2018 in the English language were identified and summarized. In the absence of larger studies, case series of n ≥ 3 were included.

Results: Sixty-three articles assessing kappa and lambda IHC and/or ISH were identified. Most focused on marginal zone lymphomas. Other lymphomas included follicle center lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma, plasmablastic lymphoma, multiple myeloma, monoclonal gammopathy of undetermined significance, and polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS). Non-neoplastic lesions included reactive lymphoid hyperplasia, cutaneous plasmacytosis, connective tissue disease, IgG4-related disease, acrodermatitis chronic atrophicans, Zoon balanitis, dermatitides, and infiltrates around epithelial dysplasias/neoplasias.

Conclusion: Kappa and lambda IHC and ISH are useful tools in the evaluation of cutaneous B-cell lymphomas and plasma cell neoplasms. The literature supports that the detection of light-chain restriction by IHC and ISH is one of the most useful findings in the differential diagnosis of reactive lymphoid hyperplasia vs B-cell lymphoma with plasmacytic differentiation.

KEYWORDS

cutaneous, immunohistochemistry, in situ hybridization, kappa, lambda, lymphoma

1 | INTRODUCTION

Atypical cutaneous lymphoid infiltrates are diagnostically challenging lesions. They often require a combination of clinical, histopathologic, immunophenotypic, and genetic features to arrive at an accurate diagnosis. Each of these features include pitfalls in interpretation and application, as reactive processes can mimic lymphomas both clinically and histopathologically and may also include a clonal B-cell and/or T-cell population. Kappa and lambda immunohistochemistry (IHC) and in situ hybridization (ISH) are useful tools in the evaluation of

cutaneous B-cell lymphomas and plasma cell neoplasms. These studies target kappa or lambda light chains in plasma cells and, to a lesser extent, B-cells. IHC for kappa and lambda on formalin-fixed, paraffin-embedded (FFPE) tissues is variably reported as cytoplasmic[1,2] or cytoplasmic and membranous[3,4] in the literature, and may depend on the antibody and technique used. In particular, enzyme digestion and heat-induced epitope retrieval techniques have been used to enhance the performance of IHC staining of neoplastic B-cells in low-grade B-cell lymphomas. In addition, the distinction between cytoplasmic and membranous staining may be difficult to discern.[1] Frozen section IHC analysis of kappa and lambda detects both cytoplasmic and membranous light chain.[1] ISH detects cytoplasmic mRNA. Flow cytometry (FC) may also be used to assess kappa and lambda ratios. FC routinely detects surface immunoglobulin and may also detect cytoplasmic immunoglobulin following a permeabilization procedure.

Kappa and lambda expression is most abundant and therefore most easily detected in plasma cells, which lose surface immunoglobulin.[5,6] As such, only light chain restricted plasma cells or cells with lymphoplasmacytoid differentiation are best detected with IHC or ISH.[2,7,8] While the precise ratios of kappa and lambda expressing cells that signify monotypia have not been defined, when a marked predominance of kappa or a predominance of lambda light chain expression is identified, a clonal population is presumed (kappa: lambda of ≥8-10[8-15] or < 0.1-0.3[8,10-18]). In contrast, non-neoplastic populations of B-cells and plasma cells characteristically include a mixture of kappa and lambda-positive cells, often with a slight kappa predominance (kappa: lambda of approximately 1-4:1-2).[9,10,19-21] As part of the American Society of Dermatopathology (ASDP) Appropriate Use Committee (AUC) Task Force, lymphoproliferative subgroup, three practicing, board-certified dermatopathologists working in academic medical centers (N.C., A.H.) or a hybrid academic/private practice (U.S.), assessed the evidence-based, peer-reviewed literature from 1967 to 2018 on the utility of kappa and lambda IHC as compared to ISH in the evaluation of cutaneous B-cell lymphomas, plasma cell neoplasms, and atypical cutaneous lymphoid infiltrates. This paper summarizes the literature for assessing light chain restriction in mucosal and cutaneous infiltrates by IHC and ISH and also briefly discusses other technologies.

2 | MATERIALS AND METHODS

2.1 | Literature review

PubMed was searched for relevant articles from 1967 to 2018 in the English language. Search terms include combinations of "cutaneous," "skin," "marginal zone lymphoma," "MALT lymphoma," "immunocytoma," "amyloidoma," "plasmacytoma," "follicular lymphoid hyperplasia," "follicle center lymphoma," "diffuse large B-cell lymphoma," "large B-cell lymphoma, leg type," "chronic lymphocytic leukemia/small lymphocytic lymphoma," "multiple myeloma," "plasmablastic lymphoma," "IgG4," "Zoon balanitis/vulvitis," "light chain," "in situ hybridization," "cutaneous pseudolymphoma," "skin pseudolymphoma," "cutaneous plasmacytosis," "kappa," "lambda," and "immunohistochemistry." In the absence of larger studies, case series of n ≥ 3 were included.

TABLE 1 Summary of articles assessing kappa and lambda immunohistochemistry and in situ hybridization in the evaluation of an atypical cutaneous lymphoid infiltrate

Total number of articles	63
Breakdown by IHC and/or ISH	
IHC	44
ISH	9
IHC and ISH	10
Breakdown by specimen processing	
Frozen	2
Formalin fixed paraffin embedded (FFPE)	49
Frozen and FFPE	5
FFPE and glutaraldehyde fixed paraffin embedded	1
FFPR and Zenker's fixed paraffin embedded	1
FFPE and B5 fixed paraffin embedded	1
FFPE and B5 fixed paraffin embedded and frozen	1
Not specified	3
Breakdown by diagnosis	
Cutaneous B-cell lymphoma, not further specified	2
Marginal zone lymphoma	39
Primary cutaneous marginal zone lymphoma*	26
Follicle center lymphoma	11
Diffuse large B-cell lymphoma	8
Diffuse large B-cell lymphoma, leg type	5
Chronic lymphocytic leukemia/small lymphocytic lymphoma	7
Mantle cell lymphoma	2
Lymphoplasmacytic lymphoma	2
Plasmablastic lymphoma	1
Plasma cell dyscrasias, including plasmacytoma	8
Multiple myeloma	7
Lymphoid hyperplasia, cutaneous and mucosal	13
Cutaneous plasmacytosis	5
Connective tissue disease	3
IgG4-related disease	2
Acrodermatitis chronica atrophicans	1
Zoon balanitis	1
Allergic dermatitis	1
Rosacea	1
Lichen planus	1
Syphilis	1
Plasma cell rich infiltrates around epithelial dysplasia/neoplasia	1
Secondary cutaneous B-cell lymphoma (not specified above)	5

[a]Includes lesions termed immunocytomas, amyloidomas, primary cutaneous plasmacytomas and cutaneous follicular lymphoid hyperplasia with monotypic plasma cells examined alone or in combination with other lymphomas.

3 | RESULTS

Sixty-three relevant articles assessing kappa and lambda IHC or ISH in the evaluation of an atypical cutaneous or mucosal lymphoid infiltrate were identified (Table 1, Table S1).[5,9-18,22-73] 44 papers evaluated IHC exclusively,[10,11,13,15,17,22-29,31,32,34,35,37,40,42,45,46,48-50,52-55,57-69,71-73] while nine papers evaluated ISH exclusively,[9,16,18,30,43,44,47,70,73] and 10 papers examined both IHC and ISH.[5,12,14,33,36,38,39,41,51,56] Two studies examined frozen tissue only,[58,65] five studies used frozen and FFPE tissue,[25,35,49,61,62] one study used formalin- or glutaraldehyde-fixed, paraffin-embedded tissue,[28] one study used formalin or B5-fixed, paraffin-embedded tissue,[50] one study used formalin or Zenker's fixed paraffin-embedded tissue,[71] one study used formalin and B5-fixed paraffin-embedded tissue and frozen tissue,[67] three studies did not specify fixation,[47,70,73] and the remainder utilized FFPE tissue.[5,9-18,22-24,26,27,29-34,36-48,51-57,59,60,64,66,68,69,72]

Most studies examined marginal zone lymphomas (MZL) of skin and mucosa (ie, extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue), either alone or in combination with other lymphomas or atypical lymphoid infiltrates (39 papers; Figure 1A-F).[5,9,11,13,14,16-18,22-24,28-33,35,38,39,41,43,44,49,50,52-54,58,60-64,66,68,69,72,73] 16 papers exclusively examined primary cutaneous marginal zone lymphoma with kappa and lambda IHC/ISH, including lesions termed immunocytomas, amyloidomas, primary cutaneous plasmacytomas, and cutaneous follicular lymphoid hyperplasia with monotypic plasma cells.[13,14,18,24,29,30,32,43,44,52-54,66,68,69,73] Other papers focused on extranodal marginal zone secondarily involving the skin or mucosa and other sites,[9] or a combination of primary and secondary MZLs.[11,23,24,28,31,50,62-64] The MZLs studied included plasma-cell-rich variants, in which plasma cells made up 50% or more of neoplastic cells.[11,18,23,24,28,31,35,41,43,50,52,54,62,63] Other lymphomas examined using kappa and lambda IHC or ISH included the relatively skin-specific entities follicle center lymphoma (FCL)[5,16,23,28,37,41,56,61,64-66] and primary cutaneous diffuse large B-cell lymphoma, leg type (DLBCL-LT).[5,22,37,41,61] One study examined primary and secondary cutaneous "T-cell-rich B-cell lymphomas."[67] Secondary cutaneous involvement by systemic B-cell lymphomas were also studied, included chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL),[5,16,25,26,39,55] mantle cell lymphoma (MCL),[23,28] lymphoplasmacytic lymphoma,[23,28] plasmablastic lymphoma,[41] "immunoblastic" lymphoma,[41,72] and cutaneous B-cell lymphoma not further classified.[66] Some studies included diffuse large B-cell lymphomas that were not fully subtyped.[16,23,28] One paper examined a variety of systemic plasma cell dyscrasias in the skin (multiple myeloma, monoclonal gammopathy of undetermined significance, Waldenström macroglobulinemia, and polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes [POEMS]).[42] Seven other papers examined cutaneous involvement by multiple myeloma.[5,15,28,41,48,70,71] Eleven papers examined kappa and lambda restriction in mucosal lesions, including oral, ocular and genital mucosa.[9,10,23,28,33,35,45,50,56,58,60] When histopathologic features were fully described, plasma cells were inconspicuous to absent in FCL,[28,37,41] MCL,[28] DLBCL,[37,41] and most cases of CLL/SLL,[25,26,39,55] and light chain restriction was recognized in some cases by weak staining of B-cells.[31,41] Non-neoplastic infiltrates examined using kappa and lambda IHC and ISH included reactive lymphoid hyperplasia (cutaneous lymphoid hyperplasia, atypical lymphoid hyperplasia, "lymphocytoma

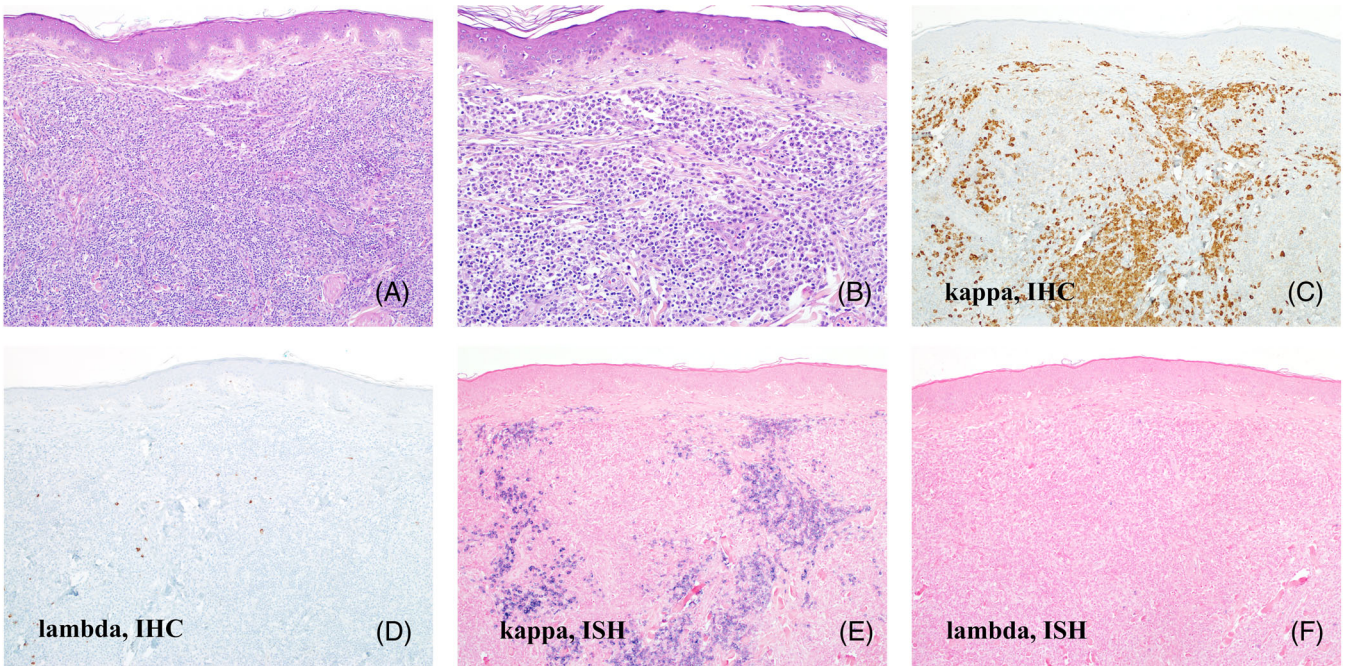

FIGURE 1 Primary cutaneous marginal zone lymphoma. Sections show a dense lymphoid infiltrate with a grenz zone and numerous plasma cells (A, B, ×100, ×200). IHC for kappa reveals numerous kappa-positive cells (C, ×100), while IHC for lambda reveals few scattered cells (D, ×100) with a kappa:lambda of >10:1. Similarly, kappa ISH marks numerous cells (E, ×100), while lambda ISH reveals rare cells (F, ×100)

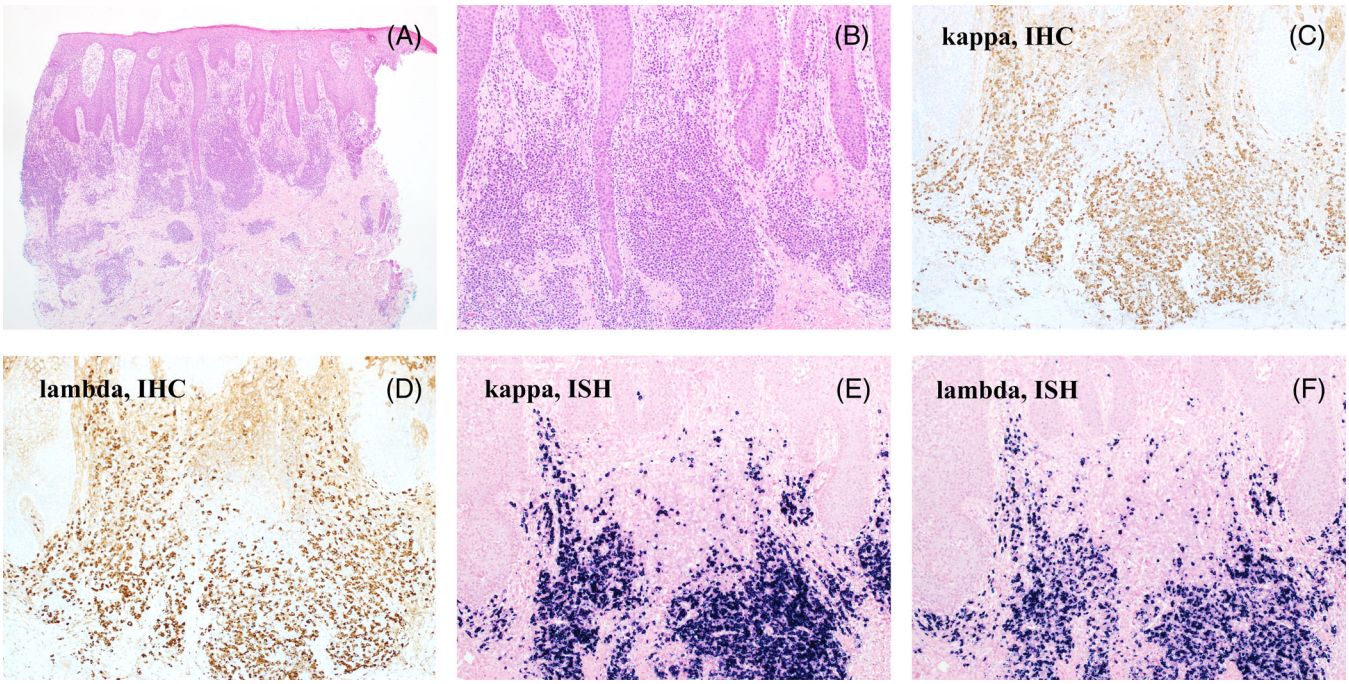

FIGURE 2 A dense, reactive infiltrate of plasma cells. Sections show psoriasiform epidermal hyperplasia with numerous associated plasma cells (A,B, ×40, ×100). Kappa IHC reveals kappa-positive cells (B, ×100) and lambda IHC shows slightly fewer lambda-positive cells (C, ×100) for a kappa:lambda of approximately 2:1. ISH similarly shows a slight predominance of kappa (D, ×100) compared to lambda (E, ×100)

cutis"),[5,16,17,22,24,27,28,41,45,56,60,64,72] cutaneous plasmacytosis,[12,34,36,40,46] connective tissue disease,[9,47,72] IgG4-related disease,[33,51] acrodermatitis chronic atrophicans,[57] Zoon's balanitis,[10] allergic dermatitis,[72] rosacea,[72] lichen planus,[72] syphilis,[72] and plasma-cell-rich infiltrates around epithelial dysplasias and neoplasias (Figure 2A-F).[72] The clinical impression was not included in many studies.[5,12,14,16,23,28-35,37,38,41,43,46,47,49-52,56-58,60,65-67,69-73]

4 | DISCUSSION

Cutaneous lymphomas are often diagnostically challenging because they show significant clinical and histopathological overlap with reactive processes and usually contain numerous reactive inflammatory cells.[21] Further complicating matters, some regions of the body, such as the ocular, oral, and genital mucosa and mucocutaneous junctions, normally have increased numbers of reactive lymphoid and plasma cells.[10] Moreover, overt lymphoma, especially MZL, may progress from pre-existing, non-neoplastic lymphoid infiltrates.[9,33,53,58,74] Small biopsy size, crush artifact, fixation issues, and distortion of lymphoid architecture by collagen and adnexal structures are common complications and may further hamper interpretation. Often a combination of clinical, morphologic, immunophenotypic, and genetic findings are necessary to render the appropriate diagnosis. Kappa and lambda ISH and IHC are often used in the evaluation of an atypical cutaneous lymphoid infiltrate, as light chain restriction in B-cells or plasma cells is highly suggestive of a clonal neoplastic process.

B-cells express surface light chain starting in the pre-B-cell stage. As they mature to plasma cells, B-cells increase the production of light chain mRNA. Plasma cells have abundant cytoplasmic light chain, but lose surface light chain. ISH detects *KAPPA* and *LAMBDA* mRNA within the cytoplasm of plasma cells and some B-cells. In contrast, IHC recognizes cellular and extracellular kappa and lambda proteins. Flow cytometry (FC) also detects light chain restriction. It is often used to detect surface light chain, but can be used to detect cytoplasmic light chain following a permeabilization procedure. ISH has been found to be superior to IHC in some studies.[6,8] In the paper by Rimsza et al., for example, the sensitivity of chromogenic ISH (CISH) was found to be 89%, while specificity was found to be 99%, when flow cytometry or IHC was used as a reference method.[6] In some conditions, IHC may display high background due to serum light chains, reactivity with follicular dendritic cells, or non-specific staining, and may show low sensitivity for one or both light chains.[1,7,8,41] In contrast, many laboratories find that ISH is less likely to show the background as it detects intracellular components, and has been reported to be more likely to recognize light chain restriction within B-cells, depending on their stage of differentiation.[6,8] While ISH may be better at detecting light chain restriction within B-cells than IHC, similar to IHC, ISH is best able to detect light chain restriction in plasma cells and cells with plasmacytic differentiation,[41] although newer techniques, such as bright field ISH may help in the detection of light chain restriction in B-cells.[16] Practically speaking, laboratories may find they have better outcomes with IHC or ISH based upon a variety of factors, including experience and platform, among other causes. Furthermore, ISH is ideally performed with separate positive and negative

controls on the tissue of interest, which can be difficult for small biopsies.

In the papers evaluated here, both kappa and lambda IHC and ISH were useful in the evaluation of atypical cutaneous lymphoid infiltrates. Detection of light chain restriction in plasma cells or B-cells supported a clonal B-cell and/or plasma cell population and a neoplastic process over an atypical reactive process. This was especially true for neoplasms with plasmacytic differentiation; however, some lymphomas without overt plasmacytic differentiation, including a subset of CLL/SLL,[5,25,26,55] FCL[16,28,37,41,61,64,65] and DLBCL[5,16,37,41] also revealed light chain restriction. While plasmacytic differentiation is expected for plasma cell neoplasms, lymphoplasmacytic lymphoma and many MZLs, CLL/SLL may show plasmacytic differentiation,[25,39] and a variety of other B-cell lymphomas rarely show an associated neoplastic plasma cell component.[75]

A handful of studies examined kappa and lambda IHC and ISH in cutaneous involvement by a plasma cell dyscrasia. Magro et al examined scleroderma-like tissue reactions in 10 patients with a preceding, concurrent or subsequent diagnosis of plasma cell dyscrasia, including monoclonal gammopathy of undetermined significance, multiple myeloma, Waldenström macroglobulinemia, and POEMS syndrome.[42] Patients presented with eosinophilic fasciitis (five cases), morphea (three cases) or systemic scleroderma (two cases). In five cases, plasma cells were light chain restricted; none of the cases showed an atypical distribution or increase in number of plasma cells compared to typical eosinophilic fasciitis and morphea. Seven other studies examined cutaneous involvement by multiple myeloma.[5,15,28,41,48,70,71] Papers with full histopathologic descriptions reported nodules to sheets of plasma cells. With the exception of three cases that could not be determined, all cases with reported kappa and lambda IHC or ISH were light chain restricted. In comparison to MZLs and other types of B-cell lymphomas and lymphoproliferative disorders, little has been examined in the realm of cutaneous plasma cell dyscrasias with respect to light chain restriction. Nonetheless, the available studies highlight that examination of kappa and lambda light chains by IHC and ISH are useful in the evaluation of cutaneous plasma cell dyscrasias and associated scleroderma-like tissue reactions.

The kappa to lambda ratio used to support a monoclonal process and diagnosis of lymphoma varied significantly, with some authors using a kappa to lambda ratio that overlapped with normal ratios (kappa:lambda >2.5-3[33,41]or lambda:kappa ≥1[41]) and others using a more pronounced ratio (kappa:lambda ≥8-10[8-15,72] or lambda:kappa >3-10[8,10-18,72]). Still, other authors used an intermediate-range (kappa:lambda >5[5,16-18] lambda:kappa >1.6-2:1[5,9,33]). Unfortunately, many studies do not specify the kappa and lambda ratio that was used to determine light chain restriction.[23-26,28-32,34-36,38-40,42-45,47-55,57-59,62-66,68-71,73] Complicating matters, universally accepted standards for kappa to lambda ratios that signify light chain restriction and monotypia have not been established.

While this review focuses on the utility of IHC and ISH for kappa and lambda light chains, these tests must be interpreted in the context of the patient's clinical and other histopathological findings. These studies are only one factor in arriving at the correct diagnosis. Reactive processes have rarely been reported to show light chain restriction. Therefore, light chain restriction may not be unequivocally diagnostic of lymphoma.[1,9,16,20,27,33,41] Some of these reported cases, however, are described with a kappa: lambda ratio within normal limits,[33,41] and some may represent a lymphoma in evolution.[9,33,41] For example, Sjögren syndrome may rarely display light chain restricted B-cells and plasma cells without the development of lymphoma.[9] Similarly, cutaneous plasmacytosis has been reported to rarely show light chain restriction.[12] These cases may represent an exaggeration of normal B-cell selection that occurs in response to an immune stimulus.[20] Unusual B-cell lymphomas or plasma cell neoplasms may include separate kappa and lambda-positive clones that mimic a normal kappa to lambda ratio.[30,76,77] Conversely, neoplastic B-cells and plasma cells may not show light chain restriction by IHC or ISH.[11,15,32,35,50,61] In some challenging cases, additional studies may be needed to assess clonality.[33,41]

FC is of limited utility for small skin tumors. However, it is generally an important tool in the evaluation of hematopoietic neoplasms and can also be used to evaluate light chain restriction in atypical cutaneous lymphoid infiltrates. FC detects light chains on the surface and/or in the cytoplasm of B-cells and detects cytoplasmic light chains in plasma cells. Examination of cytoplasmic proteins requires a permeabilization procedure. FC can be performed on skin biopsies, including punch biopsies, and requires fairly rapid transport of fresh tissue to the flow cytometry laboratory (within 4-6 hours) in Roswell Park Memorial Institute (RPMI) media. Gentle mincing/grinding of the tissue followed by filtration provide optimal results.[5,64,76] Cells are then combined with fluorescently-labeled kappa and lambda antibodies and the specimen is examined using the flow cytometer. If there are sufficient cells, FC allows the assessment of additional antigens on a given cell and it also assists in the recognition of dim antigen expression. It is reported to be more sensitive than IHC/ISH[5,6,50,64,76] and IgH gene rearrangement studies[5,64,76] at recognizing a clonal B-cell population. In comparison to IHC/ISH with a sensitivity of 37% to 55% and IgH gene rearrangement studies with a sensitivity of 39% to 43%, FC has a sensitivity of 68% to 100%.[5,64,76] However, FC has some drawbacks. It requires fresh tissue, special RPMI media, and rapid processing, and it does not include morphologic examination. A second biopsy is therefore often required for subclassification of the lymphoma. Sparse lymphoma infiltrates may not have sufficient neoplastic cells for FC studies,[5,64] and large, fragile cells as seen in DLBCL or FCL may not survive processing.[5] As cutaneous marginal zone lymphomas may show restricted plasma cells only in the deepest portion of the lesion,[13] flow cytometry theoretically could give false-negative results in superficial biopsies. Surface light chain assessment is not optimal for assessing plasma cells, and plasma cells may be underrepresented on flow cytometry, complicating the evaluation of lymphomas with significant plasmacytic differentiation.[5] Finally, FC laboratories vary in familiarity and technique in the evaluation of skin biopsies.

Gene rearrangement studies examining *IGH* or *IGK/IGL* are also helpful in the evaluation of a possible cutaneous lymphoma or plasma

cell neoplasm. This topic has recently been reviewed.[77] In summary, these studies help to support a diagnosis of lymphoma, but may be limited by insufficient or low-quality DNA, variability in the annealing of primer sets to the target sequences, somatic hypermutation, clonal heterogeneity, or variability/difficulty in the interpretation of monoclonal peaks.[77-80] Consequently, monoclonal gene rearrangements may be found in lesions that do not meet other clinical or histopathologic features of a lymphoma,[5,17,27,40,64] and neoplastic B-cell and plasma cell populations may not be recognized as monoclonal. These studies may miss clonal B-cell populations in as many as 50% of cases.[81] Gene rearrangement studies are best interpreted in the context of a case assessed in its entirety.

Next-generation sequencing (NGS) is emerging as a tool for the detection of clonal immunoglobulin light chain gene rearrangement studies.[79] Although more studies are needed, this technique may be more sensitive at recognizing a monoclonal B-cell population, even in low-density, poor quality samples. In addition, NGS can be used to simultaneously assess multiple proteins important for diagnosis or prognosis.[77,80]

In summary, there are several well-supported scenarios for the use of IHC and ISH for kappa and lambda light chains in the literature; however, important gaps in our knowledge remain. Specifically, a standard kappa:lambda threshold for determining light chain restriction in cutaneous lesions is not defined. There is an unclear relationship between light chain restriction (ie, monotypism) and monoclonality assessed by gene rearrangement studies, although these often co-occurred in the few studies that examined both. Finally, there is a lack of guidance on the sequential or concurrent utility of kappa/lambda light chain expression by IHC/ISH, flow cytometry, *IGH* and *IGK/IGL* gene rearrangement or NGS in the diagnosis and evaluation of cutaneous lymphoid infiltrates that are concerning for lymphoma. Upcoming recommendations from the ASDP AUC committee will be published separately and aim to provide guidance on the use of IHC and ISH to detect light chain restriction and utility of these tests in diagnostic dermatopathology. Importantly, there are pitfalls in the clinical, histopathologic, immunophenotypic, and genetic analysis of these cases, and accurate diagnosis relies upon a thorough assessment of the features of the case as a whole.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Hristov AC, Comfere NI, Vidal CI, Sundram U. Kappa and lambda immunohistochemistry and in situ hybridization in the evaluation of atypical cutaneous lymphoid infiltrates. *J Cutan Pathol*. 2020;47(11):1103–1110. https://doi.org/10.1111/cup.13858