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Original Contribution

Monoclonal plasma cell infiltrates in the setting of cutaneous follicular helper T cell lymphoproliferative disorders

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A B S T R A C T

There is a growing recognition that some primary cutaneous T cell lymphomas of the skin exhibit a follicular helper T cell phenotype best exemplified by primary cutaneous CD4+ small/medium sized pleomorphic T cell lymphoma. The follicular helper T cells is an evolutionary function in a common TH1 cell under the influence of other cell types most notably monocyte derived dendritic cells but also plasma cells. In addition, the skin defines a characteristic organ site of involvement for angioimmunoblastic T-cell lymphoma (AITL); the first recognized form of follicular helper T cell lymphoma.

One of the hallmarks of the follicular helper T cell lymphomas a significant degree of post germinal center B cell hyperplasia. We encountered 7 cases of primary cutaneous follicular helper T cell and four cases of AITL, in which the biopsies contained a light chain restricted plasma cell infiltrate in the skin. There were no features that suggested an atypical or more aggressive clinical course in association with the identification of this light chain restricted plasmacytic infiltrates except one case of AITL in whom a diffuse large cell B cell lymphoma subsequently developed.

There was no association with Epstein–Barr virus (EBV) infection light chain restricted plasma cell infiltrate in any of the eleven cases. The basis of these infiltrates is likely a reciprocal functional one reflecting the role of follicular helper T cells in the induction of B cell hyperplasia and the role of plasma cells as a countercheck balance controlling the extent of follicular helper T cell hyperplasia. B cell clonality, plasma cell atypia and blastic B cell transformation can occur without implying a malignant transformation.

1. Introduction

Primary cutaneous T cell lymphoma (PCTCL) comprises a heterogeneous spectrum of entities that vary clinically and histologically from a molecular, phenotypic, and cytogenetic perspective. The majority of cases of PCTCL are in the context of representing either mycosis fungoides (CTCL) or falling under the general rubric of CD30 positive lymphoproliferative disease. The third most common form of PCTCL represented by approximately 10% of all cases of PCTCL is designated as primary cutaneous pleomorphic small/medium sized T cell lymphoma [1,2] typically manifesting as a solitary lesion but at times exhibiting a multifocal pattern. With the latter setting a recently adopted designation is one of primary cutaneous follicular helper T cell lymphoma. Regarding the former entity (i.e. primary cutaneous CD4 positive small medium sized pleomorphic T cell lymphoma), the clinical presentation is reproducible with most patients, middle aged to older adults, presenting with solitary lesions typically localized to the head and neck area and or trunk. The lesions are without recurrent or progressive disease following local destructive measures such as complete excision and or radiation. The 5-year survival is in excess of 95%. Due to this apparently benign course, redefining this lymphoma as a form of indolent CD4 positive lymphoproliferative disease has been suggested whereby *the term primary cutaneous CD4+ small/medium pleomorphic T cell lymphoproliferative disorder* has supported [3,4]. These patients can develop blood, bone marrow and lymph node involvement despite a clinical course that is relatively indolent [5,6].

The discovery that these low-grade cutaneous lymphomas are forms of follicular helper T cell neoplasia was made in 2009 when Rodriquez - Pinalla and coworkers showed that neoplastic T cells in lesions that fall under the rubric of primary cutaneous CD4+ small medium sized pleomorphic T cell lymphoproliferative disorder express follicular helper T cell markers. Characteristically there is staining of at least a significant subset of the neoplastic T cells for inducible T cell costimulator (ICOS), chemokine ligand 13 (CXCL13), chemokine receptor type 5 (CXCR5), Programmed Death - 1 (PD1), and B-cell lymphoma 6 protein (BCL6), all of which are expressed by follicular helper T cells. However, apart from CXCL13 none of these markers in fact are specific for a follicular helper T cell ontogeny and can be expressed by other cell

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types [7].

CXCL13 is a very specific follicular helper T cell marker and paradoxically in most cases of follicular helper T cell lymphoma/lymphoproliferative disorder only a minor component of the neoplastic T cell populace expresses CXCL13 [8-10]. In any case of follicular helper T cell lymphoma, the extent of CXCL13 staining is significantly less compared to that observed with PD1, ICOS, and BCL6. Nevertheless in daily clinical practice a CD4 positive T cell is held to show a follicular helper T cell line of differentiation based on positive staining for PD1, ICOS and BCL6, the three most frequently used markers in determining a follicular helper T cell phenotype. They do stain a significant number of neoplastic T cells in the setting of follicular helper T cell dyscrasia be it in the context of a solitary lesion (i.e. primary cutaneous CD4 positive small/medium sized pleomorphic T cell lymphoproliferative disorder), the multifocal primary cutaneous variant (i.e. primary cutaneous follicular helper T cell lymphoma) or AITL [6].

Follicular helper T cells are derived from TH1 cells and are critical for germinal center formation, affinity maturation and the differentiation of germinal center B cells into memory B cells and high affinity antibody producing plasma cells [11]. Follicular helper B cells are defined by their unique cytokine profile and transcription factors. Naïve T cells can develop a follicular helper T cell function in the microenvironment of the monocyte derived dendritic cells by interacting with MHC/antigen on dendritic cells, an event that typically occurs in the T cell zone of the lymph node but as well dendritic cells can accumulate in the skin under conditions of immune stimulation defining a mechanism of follicular helper T cell accumulation in the skin [12-14].

The earliest follicular helper T cell expresses CXCR5 and demonstrates a decrease in the expression of CCR7. They migrate to the border of the T cells and the B cells. CXCR5 is also of importance in directing follicular helper T cells to the germinal center. CXCR5 confers the responsiveness to B cell lymphocyte chemokine CXCL13, which is produced by follicular helper stromal cells in the spleen, lymph node, and Peyer's patches [15]. Once the follicular helper T cells have migrated into the B cell anatomic niche and are interacting with B cells that are engaging in antigen presentation they become even more differentiated. CXCL13 interacts with the chemokine receptor CXCR5, which work synergistically to control the organization of B cells within germinal centers [16]. The failure to show significant positivity for CXCL13 may be attributable to an aberrant phenotype amidst the neoplastic follicular helper T cells and or a sufficiently low expression of this chemokine such that it is not detected using routine diagnostic immunohistochemical techniques. B cells that manifest the highest degree of affinity for antigen will present cognate antigen peptides to follicular helper T cells, which in turn is critical for the induction of memory B cells and plasma cells. In the presence of ICOS there is c-MAF production followed by IL-21 production [17].

IL-21, a key cytokine product of follicular helper T cells, is essential for ensuring high affinity humoral responses. Other transcription factors and cytokines including BCL6 and IL21 define the later stage cytokine makeup exhibited by the follicular helper T cells. IL21 has an autocrine function as it leads to high expression of BCL6, which defines the end point of fully functional follicular helper T cells [18-20].

The concept of concurrent B cell lymphoproliferative disease and primary cutaneous follicular helper T cell dyscrasias is not well recognized [21], although AITL with supervening clonally restricted B cell proliferations have been described. In regards to the latter, the emphasis has been on Epstein Barr virus related diffuse large cell B cell lymphoma. Since both are neoplasms of follicular helper T cell origin it would seem that pathophysiologic mechanisms that are implicated in the setting of AITL could also apply to this primary cutaneous lymphoproliferative lesion.

We report 7 cases of primary cutaneous follicular helper T cell lymphoproliferative disease represented by cases of primary cutaneous CD4+ small/medium sized T cell lymphoproliferative disease with a supervening light chain restricted plasma cell infiltrate. We also present four cases of AITL where the skin biopsies showed clonally restricted post germinal center lymphoplasmacytic B cell infiltrates in the absence of EBV infection accompanied by a variable neoplastic T cell response. Pathophysiologic mechanisms are explored.

2. Materials and methods

A natural language search was done of the database ranging from 2006 to 2018 to identify cases of follicular helper T cell lymphoma including cases with a primary diagnosis of primary cutaneous CD4+ small/medium sized pleomorphic T cell lymphoma where there was evidence of a light chain restricted plasma cell infiltrate. All of the cases were received in consultation by CMM. In each case a careful light microscopic assessment along with phenotypic and molecular studies had been performed as part of the routine diagnostic evaluation in each case. In the search of our database, we also came across four cases of AITL presenting in the skin whereby there was evidence of light chain restricted plasmacytic infiltrates. Among the archival stained material available for review were slides stained for EBER CD2, CD3, CD4, CD5, CD7, CD8, PD1, BCL6 ICOS, CXCL13, NFAT, CD20, CD79a, CD21, CD23, Kappa, and Lambda. Molecular T and B cell studies were conducted on the majority of the cases as part of the routine evaluation of the cases.

2.1. Clinical summaries (see Table 1)

The patients diagnosed with primary cutaneous CD4 positive small medium pleomorphic T cell lymphoproliferative disorder were represented by four males and three females. The patients ranged in age from 31 years to 95 years (mean age of 65 years, median age of 63 years). All presented with a solitary infiltrative plaque and or nodule on the neck (3), scalp (2), cheek (1), and chest (1) treated with complete excision. Two patients had complete excision followed by radiation. None of the patients experienced new or skin disease, or disease at extracutaneous sites. The follow up period ranged from 1 to 4 years; the mean follow up time period was 2 years. All patients are alive and well except one patient who died of natural age related causes at the age of 98.

In addition our study included four patients with AITL in whom skin lesions developed that showed light chain restricted plasmacytic infiltrates in a background of AITL. The patients ranged in age from 58 to 81 years of age (median and mean age of 68). All four patients had extensive cutaneous disease (Fig. 10, 11, 12). All four of the patients had significant extracutaneous disease with lymph node biopsy proven AITL. Three of the cases had been received by one of the authors in consultation; three of the 4 cases were treated at a tertiary care center. A summary of the clinical features of these cases is presented in Table 1. In case 8 the patient had been on long term anticonvulsant therapy (Lamotrigine) since childhood when he developed a lupus-like Syndrome with generalized papules plaques, polyarthritis and splenomegaly. A monoclonal gammopathy antedated the illness.

Lymphadenopathy became apparent after his prednisone was reduced. Despite a positive response of his rash to chemotherapy he continues to have cutaneous disease including more recent biopsies showing a significant degree of B cell infiltration. Case 9 presented with disabling progressive sero-negative polyarticular arthritis followed by skin nodules and plaques. Following the skin biopsy imaging studies disclosed extensive disease involving the spleen, lymph node, lung, liver and subcutaneous tissue. He had a positive response to chemotherapy but biopsy of a new skin tumor and a perirenal mass showed or EBV + CD30+ diffuse large B cell lymphoma.

2.2. Light microscopic findings (see Table 2)

In all biopsies procured from lesions that fell into the primary cutaneous category, there was a superficial and deep lymphocytic

Table 1
Clinical presentation of patients.

Case	Age/sex	PCTCL	ECTCL	Lesions	Location	Treatment	Outcome
(1)	95/M	Yes	No	Solitary	Neck	Excision	CR: 3 yr Died of old age at 98
(2)	51/F	Yes	No	Solitary	Cheek	Excision/local radiation	CR: 4y FU
(3)	81/M	Yes	No	Solitary	Scalp	Excision	CR: 2y FU
(4)	31/M	Yes	No	Solitary	Scalp	Excision	CR: 2y FU
(5)	76/M	Yes	No	Solitary	Neck	Excision	CR: 1y FU
(6)	43/F	Yes	No	Solitary	Chest	Excision	CR: 1y FU
(7)	88/F	Yes	No	Solitary	Neck	Excision/local radiation	CR: 2y FU
(8)	58/M	Yes	Yes	Multilesional	Trunk	Medication	Living with the disease
(8)	58/M	Yes	Yes	Multilesional	Trunk	Medication	Living with the disease
(8)	58/M	Yes	Yes	Multilesional	Upper arm	Medication	Living with the disease
(8)	58/M	Yes	Yes	Multilesional	Shoulder	Medication	Living with the disease
(9)	67/M	Yes	Yes	Multilesional	Thigh	Medication	Living with the disease
(10)	68/M	Yes	Yes	Multilesional	Upper arm	Medication	Living with the disease
(11)	81/M	Yes	Yes	Solitary	Left thigh	Medication (1 cycle of CD30-directed antibody drug conjugate)	Recurrence after 18 months (two lesions, abdomen and thigh)

M, male; F, female; PCTCL, primary cutaneous T cell lymphoma; ECTCL, extra cutaneous T cell lymphoma; CR, complete resolution; FU, follow up.

Table 2
Light microscopic findings for each case.

Case	Architecture	Depth	Follicle	Eccrine	Vessel	SC	Nerve	T-cell cytology	B-cell cytology	Plasma cell	Vascularity	Eosinophil	GI
(1)	D/N	S/D	No	Yes	Yes	No	Yes	Small/intermediate	Small	Low grade Atypia	No	No	Yes
(2)	D/N	S/D	Yes	No	No	No	No	Small/intermediate	Small	Yes	No	No	Yes
(3)	N	S/D	Yes	No	Yes	No	No	Small/intermediate/large	Small	Yes without Atypia	No	No	Yes
(4)	N	S/D	Yes	Yes/s	Yes	No	No	Small/intermediate/large	Small	Yes without Atypia	No	No	Yes
(5)	N	S/D	Yes	Yes	Yes	No	No	Small/intermediate/large	Small	Yes with Atypia	Yes	No	Yes
(6)	N/D	S/D	No	No	No	Yes	No	Small/intermediate/large	Small	Yes with Atypia	No	No	Yes
(7)	N/D	S/D	No	No	Yes	Yes	No	Small/intermediate/large	Small	Low Grade Atypia	No	No	Yes
(8)	N/D	S/D	Yes	Yes	Yes	Yes	No	Small/intermediate	Small	Yes without atypia	No	No	Yes
(8)	N/D	S/D	No	Yes	Yes	Yes	No	Small/intermediate	Small	Yes with atypia	No	No	Yes
(8)	N/D	S/D	Yes	Yes	Yes	Yes	No	Small/intermediate/large	Large	Yes	No	No	Yes
(8)	N/D	S/D	Yes	No	Yes	Yes	Yes	Small	Small/Large	No	No	No	Yes
(9)	N/D	S/D	Yes	Yes	Yes	Yes	Yes	Small	Small	Yes with mild atypia	No	Yes	No
(10)	N/epidermotropic	S	No	Yes	Yes	No	Yes	Small/intermediate	Small	Yes, mild atypia	No	No	Yes
(11)													

S, superficial; d, deep; S/D; superficial/deep; SC, subcutaneous; GC, germinal center; GI, granulomatous inflammatory.

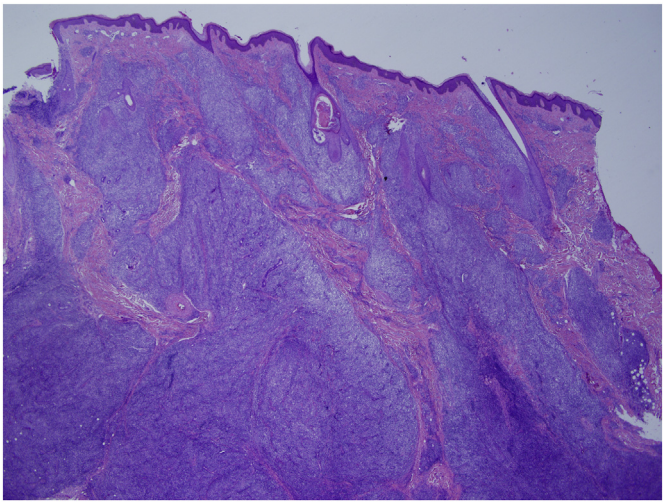

Fig. 1. The patient is a 31-year-old male who presented with a solitary lesion on the scalp. His biopsy demonstrates a striking pan dermal tumefactive multinodular lymphocytic infiltrate (case 4).

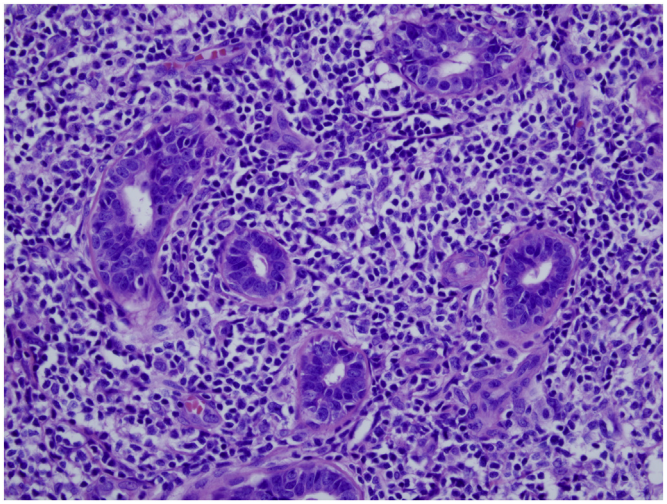

Fig. 2. There is a distinctive pattern of eccrinotropism. The infiltrates permeate the advential dermis of the eccrine coil resulting in a nodular expansion of the eccrine coil. Note the irregular distortion of the ducts and glands. There is also focal permeation of the ducts and glands by atypical lymphocytes (case 4).

infiltrate that assumed a nodular growth pattern; in one case the infiltrate extended into the subcutaneous fat (Fig. 1). In 3 of the 7 cases the infiltrate assumed a diffuse pattern as well. There was a tendency for the infiltrate to be closely apposed to and frankly infiltrative of hair follicles in 5 of the cases and the eccrine coil in 4 cases with intraepithelial syringotropic extension in 2 cases (Fig. 2). The eccrine coil involvement was a characterization and frequently resulted in a nodular distortion of the eccrine apparatus. In 6 cases the infiltrate was accentuated around vessels and while permeative of the vessel wall of

Table 3
Phenotypic profile.

Case	CD3/CD20	CD4/CD8	BCL6	PD1	CD7	CD5	NFAT	CD23	CD21	K/L	CD20/CD79a	Other
(1)	> 10/1	> 5/1	+ T cells	+	Reduced 95%	NR	NP	Negative	NP	< 1/10	1 (no decrease)	
(2)	3/1	> 5/1	+ T cells	+ T cells	Reduced 80%	NR	NP	+	NP	10/1	1 (no decrease)	20% stain FoxP3
(3)	3/1	> 4/1	+ T cells	+ T cells (40%)	NP	NR	NP	NP	NP	10/1	1 (no decrease)	
(4)	3/1	5/1	+ T cells	+ T cells (large cells)	Minimal 20% reduced	NR	NP	NP	Focal +	1/10	20% decrease CD79a	
(5)	3/1	5/1	+ T cells	+ T cells	No reduction	30% reduction	+ T cells	Negative	Negative	1/3	1 (no decrease)	
(6)	2/1	4/1	+ T cells	+ T cells	20% reduction	NR	+ T cells	Negative	Negative	1/3	1 (no decrease)	Focal EBV +
(7)	10/1	> 5/1	+ T cells	+ T cells	30% reduction	30% reduction	+ T cells	Negative	Negative	> 5/1	No loss of CD79a	
(8)	NP	2/1	+ T cells	+ T cells	NR	NR	+ T cells (5%)	NP	NP	5/1	1 (no decrease)	Tox in atypical cells
(8)	3/1	1/1	+ T cells	NP	NR	NR	NP	Negative	Negative	1/3	1 (no decrease)	Minor subset of B cells express CD30
(8)	1/1	1/1	NP	30% T cells	NR	NR	NP	Negative	Negative	1/2	1 (no decrease)	30% CD30 staining
(8)	3/1	1/1	30% cells	15% T cells	NR	50% reduction	NP	Negative	Negative	1/10	1 (no decrease)	
(9)	1/2	5/1	+ T cells	+ T cells	NR	30% reduction	NP	Negative	Negative	10/1	1 (no decrease)	
(10)	NP	3/1	+ T cells	+ T cells	50% reduction	50% reduction	+ T cells	NP	NP	½	NP	Decrease CD3
(11)	1/1	5/1	+ T cells	+ T cells	NR	NR	NP	NP	NP	5/1	1 (no decrease)	

NP: not performed; NR: no reduction.

Fig. 3. A significant component of the infiltrate established to be of T cell lineage manifests a follicular helper T cell phenotype. Illustrated is the PD1 stain demonstrating a number of positive cells (case 4).

vasculitis were not observed.

From a cytomorphologic perspective the infiltrate was a heterogeneous one comprising a mixture of small, intermediate and larger sized lymphocytes. The lymphocytes exhibited nuclear hyperchromasia with nuclear contour irregularity including nuclear blebs although without the classic cerebriform cytology observed in mycosis fungoides. The larger lymphocytes were present in a single cell and focally aggregated fashion but defined the minor cell populace never exceeding > 30% of the infiltrate. In all cases there was a significant degree of histiocytic infiltration hence imparting a granulomatous quality to the infiltrate. There was a smattering of eosinophils but in no case were eosinophils prominent.

In each case, there was a conspicuous plasmacytic component accompanied by a variable degree of non-plasmacytic B cell hyperplasia including one case where there was infiltration of the outer root sheath epithelium by B cells. The plasma cells showed low-grade atypia in 4 of the 7 cases. The plasma cells were accentuated around blood vessels and also assumed a sheet like arrangement and were most conspicuous adjacent to the zones of T cell rich nodular lymphocytic infiltration. Well-defined germinal centers were not seen in any of the cases. In one case the extent of atypia amidst the B cells including a number of significantly dysplastic plasma cells was more in keeping with a true concurrent T and B cell lymphoma. This one case was the only case in our series that showed both T and B cell clonality.

Overall, the morphology in the biopsies of AITL closely recapitulated what was uncovered in the primary cutaneous cases although there were additional features not encountered in the primary cases and or at least not to the same degree (Figs. 5–7). One distinguishing feature was the frequency of subcutaneous involvement in the cases of AITL. One of the cases of AITL was remarkable for the extent of angiocentric immunoblastic large cell B cell infiltration especially in the superficial aspect of the biopsy becoming conspicuous after his neoplastic T cell component became attenuated following T-cell directed chemotherapy.

In the third and fourth cases of AITL (cases 10,11), there was a significant degree of large cell T cell infiltration in the superficial dermis while deeper-seated nodular foci of monomorphic differentiated plasma cell infiltration were observed. In two cases of AITL there a concomitant vascular component characterized by a proliferation of small capillaries and venules. In this third case of AITL (case 9) while the initial biopsy had only a few lambda light chain restricted plasma cells a subsequent biopsy performed a few months later showed a post germinal center diffuse large B cell lymphoma exhibiting lambda light

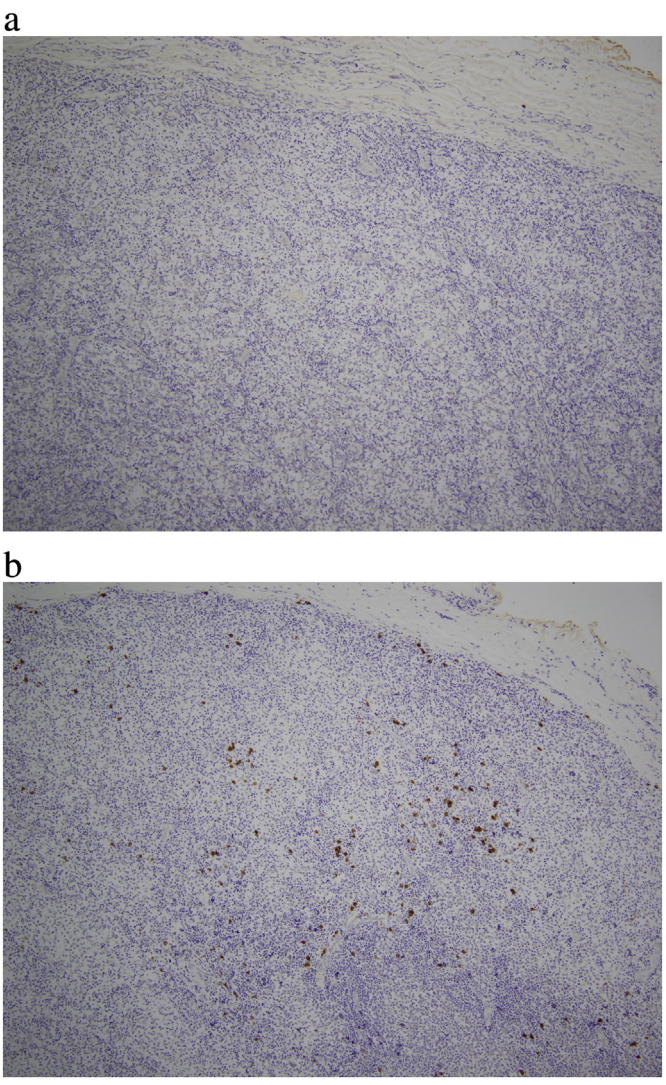

Fig. 4. There are scattered plasma cells amidst this dominant T cell infiltrative process. The plasma cells are well differentiated without dysplastic features. There is evidence of clear-cut lambda light restriction. In Fig. 4a, there are no cells that stain positively for kappa while in Fig. 4b the plasma cells stain positively for lambda indicative of lambda light chain restriction (case 4).

chain restriction, raising speculation regarding its origin from the earlier plasmacytic infiltrate which while not atypical exhibited a similar pattern of light chain restriction.

2.3. Phenotypic findings (see Table 3)

In all primary cutaneous cases there was a predominance of T cells over B cells, whereby the T to B cell ratio ranged from 2:1 up to 10:1. In most cases, the T to B cell ratio was in the 3:1 range. The B cell component that was highlighted was in the context of small nodular aggregates and singly disposed lymphocytes that were primarily small in the 7 to 9 μm size range, but as well larger blastic elements were seen. The B cells were intermingled with the dominant T cell component. Because of the very cellular and diffuse nature of the infiltrate without any distinctive B cell features such as germinal centers an obvious cytomorphologic distinction between the neoplastic T cells and cells of putative B cell derivation was very difficult based purely on light microscopic assessment. The typical zonation encountered in a pseudolymphoma was not observed. Conspicuous germinal centers were not seen in any of the cases.

There was a predominance of CD4 T cells over those of the CD8

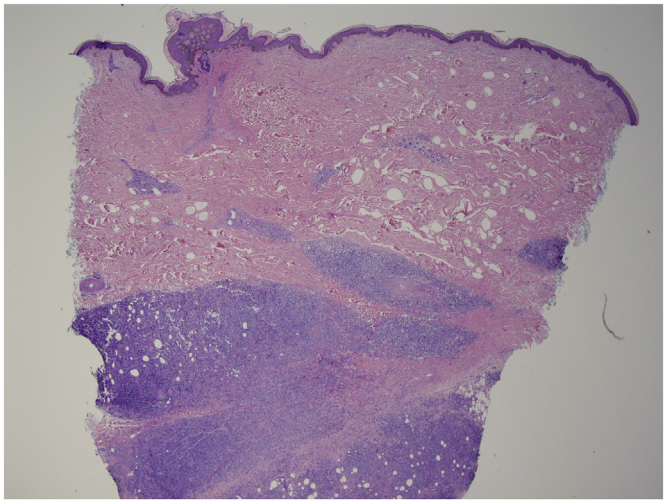

Fig. 5. The patient is an 81-year-old man with an established history of angioimmunoblastic T-cell lymphoma. The patient was in remission but then in 2016 presented with a solitary lesion on the thigh. The patient developed a cutaneous recurrence 18 months later along with an additional lesion on the abdomen (case 11). The biopsy shows a striking mid and dermal atypical lymphocytic infiltrate assuming a confluent diffuse and nodular growth pattern (case 11).

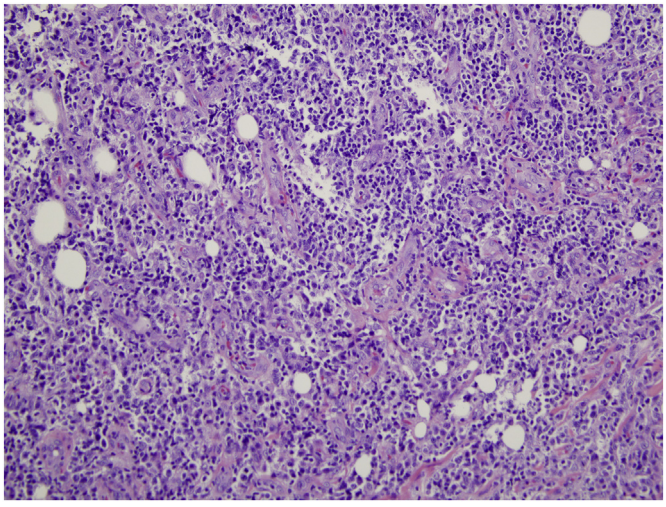

Fig. 6. The infiltrate shows severe atypia amidst the lymphocytes. There is a distinctive pattern of neovascularization apparent at this power (case 11).

subset; the ratio was elevated at 5:1 or higher in all cases. In all cases a number of the T cells showed positivity for BCL6 and PD1, typically representing 30% to 40% of the T cell infiltrate; the staining patterns between BCL6 and PD1 were similar, highlighting the same cells (Fig. 3). In addition a subset of the cells highlighted by BCL6 and PD1 showed nuclear staining for nuclear factor of activated T-cell (NFAT). In cases where ICOS was performed the staining pattern more or less mirrored that observed for NFAT and BCL6. CXCL13 and CD10 were conducted in some cases and showed focal staining that was much less than that observed for PD1 and BCL6.

There was a decrement in staining for CD7 in 5 of the 7 cases tested but in all but two the reduction was minimal, in the 20 to 30% realm. Two of the 7 cases tested showed a reduction in staining for CD5 in the 30% realm while in the remaining cases there was no diminution in staining.

There was evidence of a light chain restricted plasma cell infiltrate which was lambda restricted in 4 (Fig. 4a and b) and kappa light chain restriction in 3 (Fig. 9). In two cases there was minimal CD21 staining

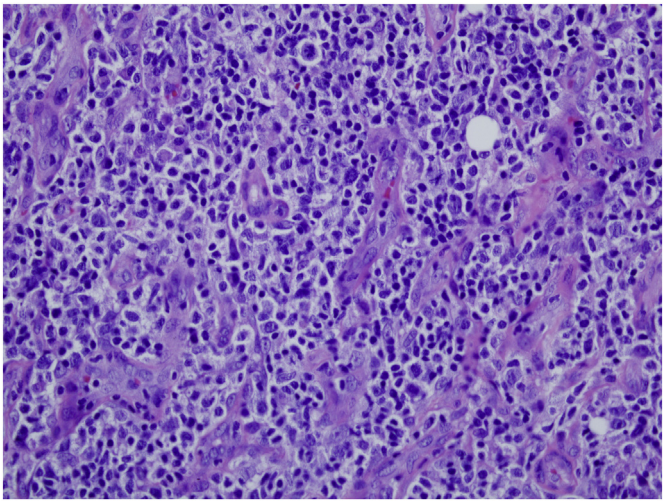

Fig. 7. Cytomorphologically the lymphocytes represent a combination of small, intermediate and larger lymphoid cells. At this power there is significant nuclear hyperchromasia and nuclear contour irregularity although lymphocytes with a frankly cerebriform cytology are not seen. Scattered mitotic figures are apparent (case 11).

possibly representing the residuum of germinal centers although none were discernible on routine light microscopic examination.

In the cases that fell under the rubric of AITL the findings were similar to those seen in the primary cutaneous setting. A significant component of the infiltrate was CD4 positive manifesting positivity for PD1 and BCL6 along with variable staining for NFAT and ICOS, CD10, and CXCL13 (Figs. 8a, b, c, 13a, b). There were some noteworthy differences with the primary cutaneous cases. In particular, while only 4 cases were examined there was a greater extent of B cell hyperplasia in the cases of AITL compared to primary cutaneous cases. In one case, the T to B cell ratio was reversed and in one case the ratio was equal (Fig. 13a, b, c). In this latter case, the initial biopsy prior to any initiation of treatment showed a striking T cell dominance with a minimal B cell component. In contrast, in the primary cutaneous settings this relative extent of B cell hyperplasia was not seen. In three of the four cases, there was no significant loss in the expression of CD7. In one case the reduction was 50% in the dermis and 90% in the epidermis where the pattern mimicked mycosis fungoides. One case showed a very extensive pattern of CD21 follicular dendritic cell hyperplasia mirroring the pattern encountered in the lymph node. While in the primary cutaneous setting the extent of CD4 T cell infiltration always exceeded that for CD8 in a ratio that was higher than the normal ratio in one case of AITL the extent of CD8 T cell infiltration was significant resulting in a CD4 to CD8 ratio of 1:1(case 8). There was lambda light chain restriction in two cases and kappa light chain restriction in two cases. However in one case one biopsy showed equalization of the kappa to lambda ratio therefore suggesting an emerging light chain restricted lambda light chain restricted infiltrate while in another biopsy performed three months after the commencement of T cell directed therapy the immunoblastic and plasmacytic component was kappa light chain restricted; there was no staining for lambda. There was florid CD21 hyperplasia in one case of AITL (Figs. 8d, 13d, e). In one of the cases showing lambda light chain restriction (case 9) even though the plasma cells were few in number and rather bland the patient subsequently developed an EBV positive diffuse large cell B cell lymphoma exhibiting a post germinal center phenotype with evidence of lambda light chain restriction.

2.4. Molecular studies (see Table 4)

Clonality studies were conducted in 5 cases and in each case the studies were positive for evidence of T cell clonality while the B cell molecular studies showed a polyclonal result; in one case there was

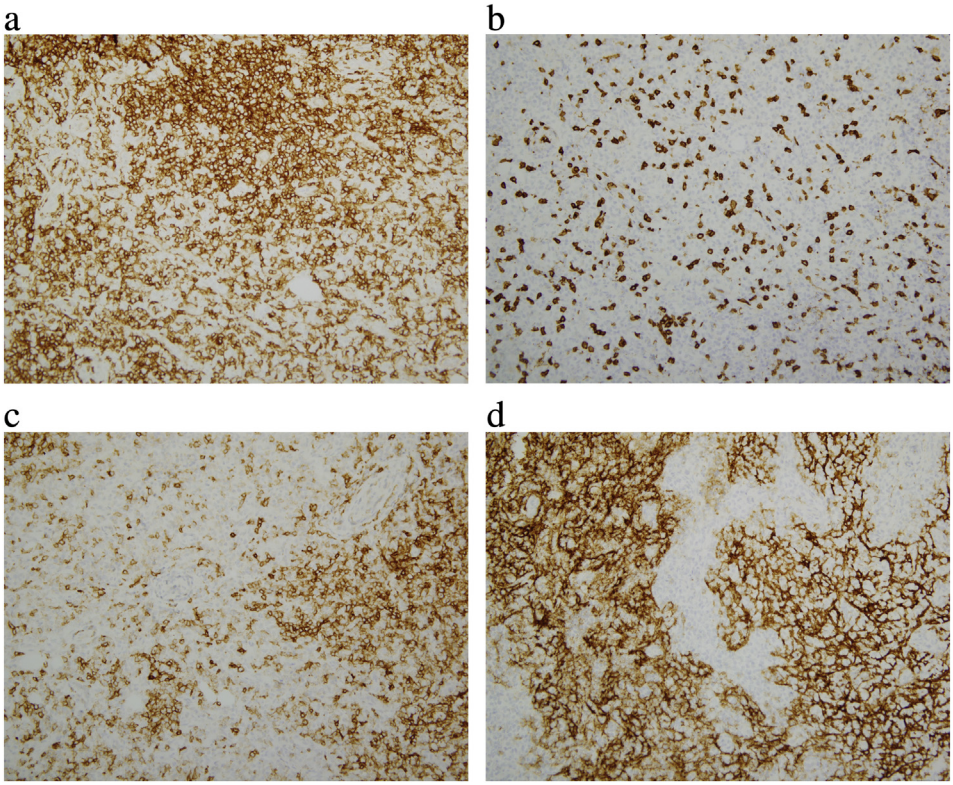

Fig. 8. The infiltrate is highlighted by CD4 (8a). Only a minor CD8 T cell component is present (8b). A number of the T cells show a follicular helper T cell phenotype as revealed by the extent of staining for PD1 (8c) and BCL6 (not illustrated). A striking pattern of reactive CD21 is observed (8d) (case 11).

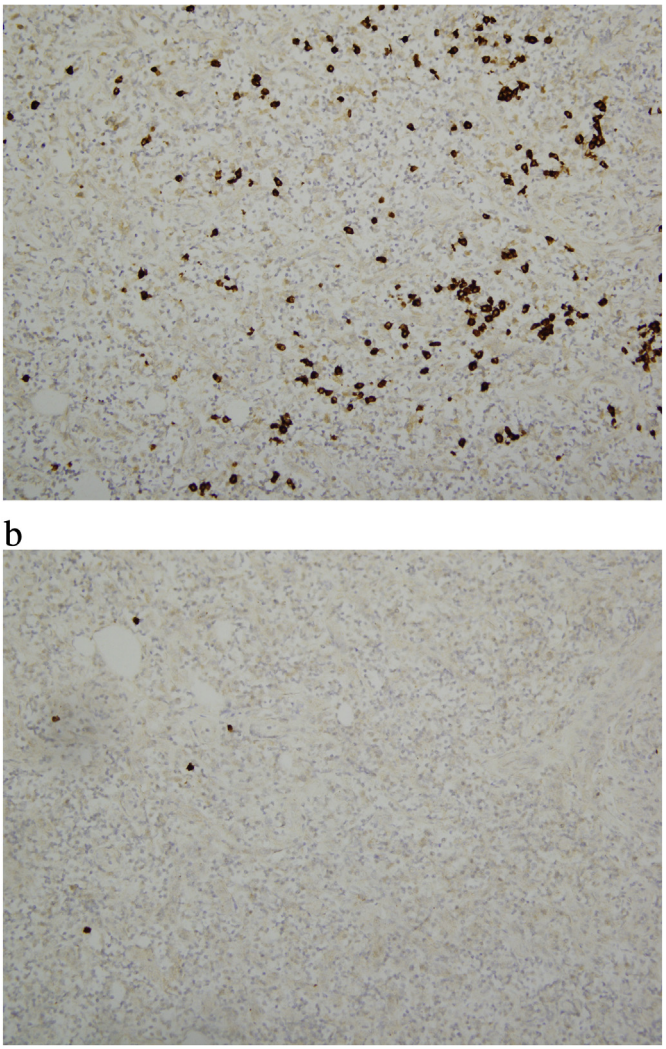

Fig. 9. The biopsy showed a plasmacytic infiltrate without obvious atypia amidst the plasma cells. The plasma cells show clear-cut light chain restriction for kappa (9a). The lambda preparation is essentially negative (9b) (case 11).

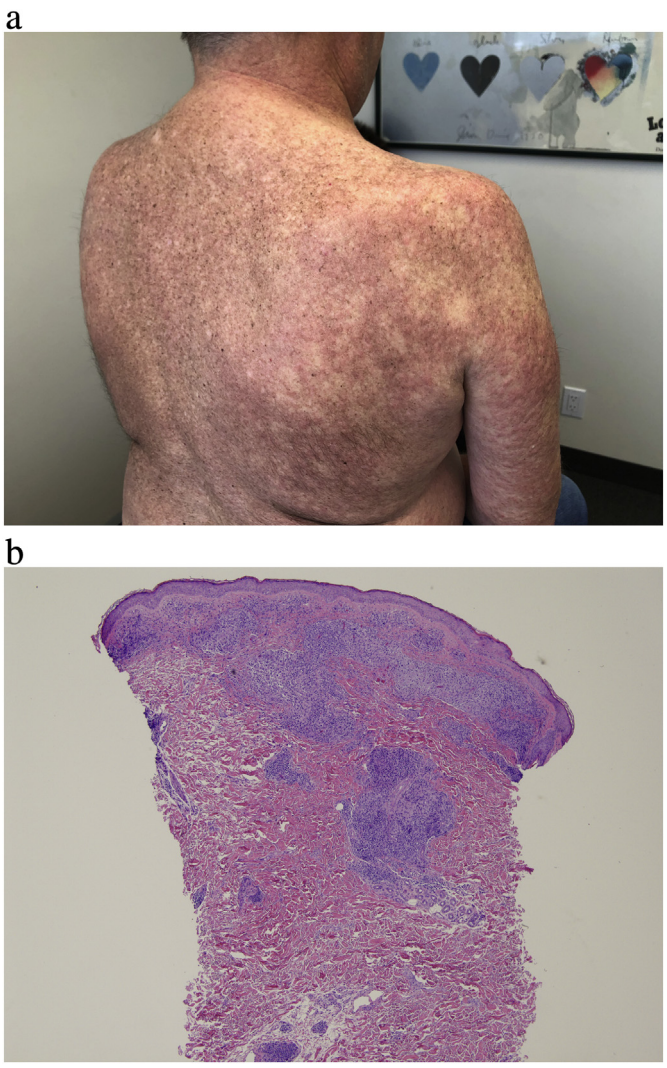

Fig. 10. The patient is a 57-year-old male with an established diagnosis of angioimmunoblastic lymphoma. The patient has extensive cutaneous disease, which has shown some partial responsiveness to chemotherapy administration. The patient is scheduled to receive a stem cell transplant (10a). A biopsy shows a superficial to mid dermal coalescing nodular lymphocytic infiltrate demonstrating some accentuation around vessels therefore defining a lymphomatoid vascular reaction (10b) (case 8).

evidence for both T and B cell clonality. See Table 4. In one case the same T cell clone was isolated from each biopsy.

3. Discussion

We have presented 7 cases of classic primary cutaneous CD4 positive small medium sized pleomorphic T cell lymphoma/lymphoproliferative disorder and 4 cases of AITL. The uniqueness of the 11 cases was in the presence of light chain restricted plasmacytic B cell infiltrates. In the former category of primary cutaneous B cell lymphoproliferative disease, all of the cases presented with a solitary nodule without any evidence of extracutaneous lymphoproliferative disease. All of these patients were treated with complete excision with or without radiation without incident. There was no evidence of recurrent disease nor was there the development of additional sites of cutaneous and or extracutaneous involvement. In contrast, patients with AITL had widespread cutaneous and extracutaneous disease. In all cases the cutaneous infiltrates were predominated by a nonepidermotropic diffuse and nodular CD4 dominant lymphocyte rich infiltrate comprising small to intermediate sized atypical CD4+ lymphocytes exhibiting a follicular helper T cell phenotype infiltrate in a significant subset of the T cells. The follicular helper T cell phenotype was inferred by the extent of staining for PD1, ICOS, BCL6 and CXCL13. However, the cases of AITL differed from the classic morphologic and phenotypic profile of follicular helper T cell lymphoma due to the presence of a light chain restricted plasmacytic infiltrate. As the plasma cells could show atypia and as well one case had immunoblastic and plasmablastic features, the presence of this light chain restricted plasmacytic infiltrates was a source of confusion especially in regards to the exact classification of the infiltrate (i.e. B cell versus T cell lymphoproliferative disease versus concurrent T and B cell lymphoproliferative disease). The main considerations were in the context of 1. a composite T and B cell lymphoma, 2. A T cell rich marginal zone lymphoma and finally 3. A primary cutaneous small medium sized pleomorphic T cell lymphoma or AITL with an emerging light chain restricted infiltrate of undetermined significance but probably reactive in nature.

The first lymphoproliferative disorder recognized to be of follicular helper T cell derivation was *angioimmunoblastic lymphadenopathy with dysproteinemia*, a term coined by Frizzera and Rappaport in 1974 [22].

Patients typically present with evidence of multiorgan disease oftentimes with laboratory and clinical autoimmune findings. This may present with a myriad of symptoms and signs including fever, malaise

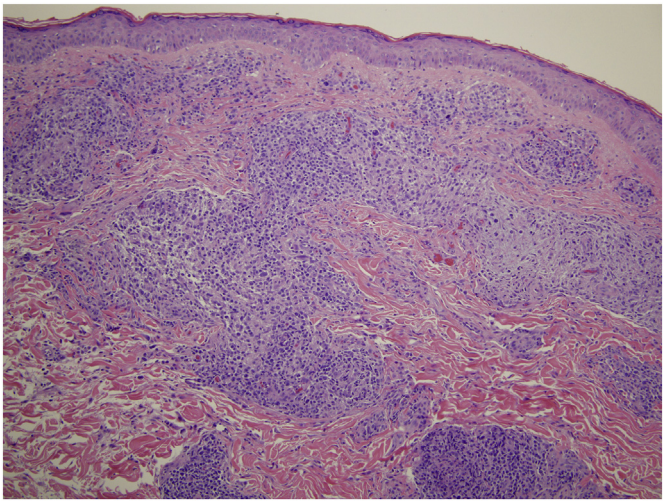

Fig. 11. Higher power magnification of the infiltrate shows the extent of lymphoid atypia even at this power. There is a narrow grenz zone that separates the infiltrate from the epidermis. It is a nonepidermotropic infiltrate that shows accentuation around vessels (case 8).

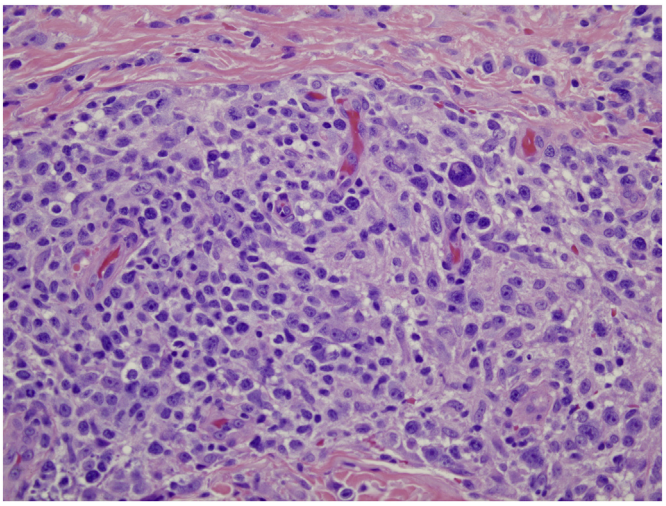

Fig. 12. The cells include a number of larger blastic appearing cells along with smaller atypical lymphocytes. The blastic cells are primarily of B cell lineage. While manifesting a transformed morphology with evidence of light chain restriction the B cell component is not interpreted as being malignant. The minor cell populace is the atypical T cell component that appears to have undergone significant attenuation with chemotherapy intervention (case 8).

and weight loss, generalized lymphadenopathy, hepatosplenomegaly, oligoarthritis or polyarthritis, Coombs positive hemolytic anemia and polyclonal hypergammaglobulinemia [23,24]. An idiosyncratic T cell driven clonal response to drug hapten likely defines a critical trigger to its development whereby drugs include penicillin; doxycycline, sulfonamide, dilantin, macrolides, allopurinol, and halothane [25,26] are among potential triggers.

Mutations characteristic of AITL namely TET2, IDH2, DNMT3A and RHOA have been detected in at least a subset of cases although practically speaking this type of mutational assessment is not performed as part of the routine evaluation of atypical lymphocytic infiltrates [27].

It was Dorfman and coworkers who discovered that the ontogeny of this lymphoma was one of follicular helper T cell derivation based on the observation of BCL6, CD10 and PD1 expression in the neoplastic T cells. PD-1 is a marker of germinal center-associated T cells and AITL [28]. They emphasized that the same cell type surrounded the neoplastic L and H cells in nodular lymphocyte predominant Hodgkin lymphoma. In addition, it has been shown that plasma cells including transformed plasma cells are capable of promoting follicular helper T cell differentiation reflective of the effects of IL-6 in the induction of a follicular helper T cell phenotype [29]. Presumably, the same pathogenetic mechanisms underlying B cell hyperplasia in the setting of AITL would be implicated in cases of primary cutaneous follicular helper T cell lymphoma including cases of primary cutaneous CD4 positive small/medium sized pleomorphic T cell lymphoma.

Atypical B cell proliferations in the setting of follicular helper T cell lymphoma have been reported primarily in the setting of AITL.

However the majority of monoclonal B cell proliferations in the setting of T cell lymphoma are characteristically associated with EBV infection where their most common occurrence is in the context of AITL. In the EBV associated clonal B cell proliferations of T cell lymphoproliferative disease, there are distinctive patterns that are recognized: small clusters of large atypical B cells amidst the atypical T cells, an effacing infiltrate of large atypical B cells, smaller B cell or plasmacytic proliferations and finally Reed Sternberg like proliferations. In addition, at least in the setting of AITL clonality from a B cell perspective occurs in almost half of cases even though one cannot see an obvious light microscopic equivalent in terms of obvious atypical B cell infiltration [30,31]. In many of the cases the proliferations while appearing somewhat atypical and at times extensive are without disease progression to overt B cell lymphoma. The EBV associated B cell lymphomas are reported to display a latency II or latency III pattern of EBV protein expression resembling EBV B cell proliferations in immunosuppressed individuals [32]. In the study by Zaki and co-workers the authors reported T and B cell clones in 77.6% and 17.6% of patients with peripheral T cell lymphoma and precursor T lymphoblastic lymphoma [33]. They examined 76 cases and correlated clonality results with EBV status. B cell clones were primarily found in peripheral T cell lymphomas not otherwise specified and AITL. Immunodeficiency reflective of iatrogenic and endogenous immune dysregulation is likely a critical factor (Figs. 11 and 12).

Over and above EBV positive B cell proliferations are those clonal proliferations of B cells in the setting of peripheral T cell lymphoma that are not EBV related. The only series to date devoted to this topic was by Balague and coworkers. They described 15 cases of peripheral T cell lymphoma with clonal EBV negative B cell proliferations. Ten of the cases were in the context of nodal T cell lymphoma while 5 of the cases were primary cutaneous lymphomas. In two of the primary cutaneous cases the patients had primary cutaneous CD4 positive small/medium sized pleomorphic T cell lymphoma [34]. The main types of proliferations were characterized by plasma cells intermingled with the atypical T cell component, Reed Sternberg-like B cells amidst the atypical T cell component and finally an overt B cell lymphoma typically in the context of representing plasmablastic large cell B cell lymphoma. The monoclonal differentiated plasmacytic components similar to our 8 cases was observed in two of their cases that they classified as primary cutaneous CD4 positive small medium sized pleomorphic T cell lymphoma. In their cases, the plasma cells were always identified at the sites of T cell infiltration. They could be intermingled with the atypical B cell component or they were present as small clusters characteristically distributed more peripherally in the zones of atypical T cell infiltration. Uncommonly, there was the development of frank plasmacytoma characterized by sheets of plasma cells that displaced the T cell lymphoma component.

There are additional papers describing cutaneous EBV negative clonal plasma cell infiltrates including cases with isotype switching occurring in the setting of AITL primarily representing anecdotal case reports. The proliferations did not necessarily correlate with T cell disease as they could develop when there was a positive response to treatment and or they could become prominent with only a minimal T cell component despite progressive T cell disease. In some cases the localized infiltrates presaged an aggressive clinical course including the development of diffuse large cell B cell lymphoma in the lymph node

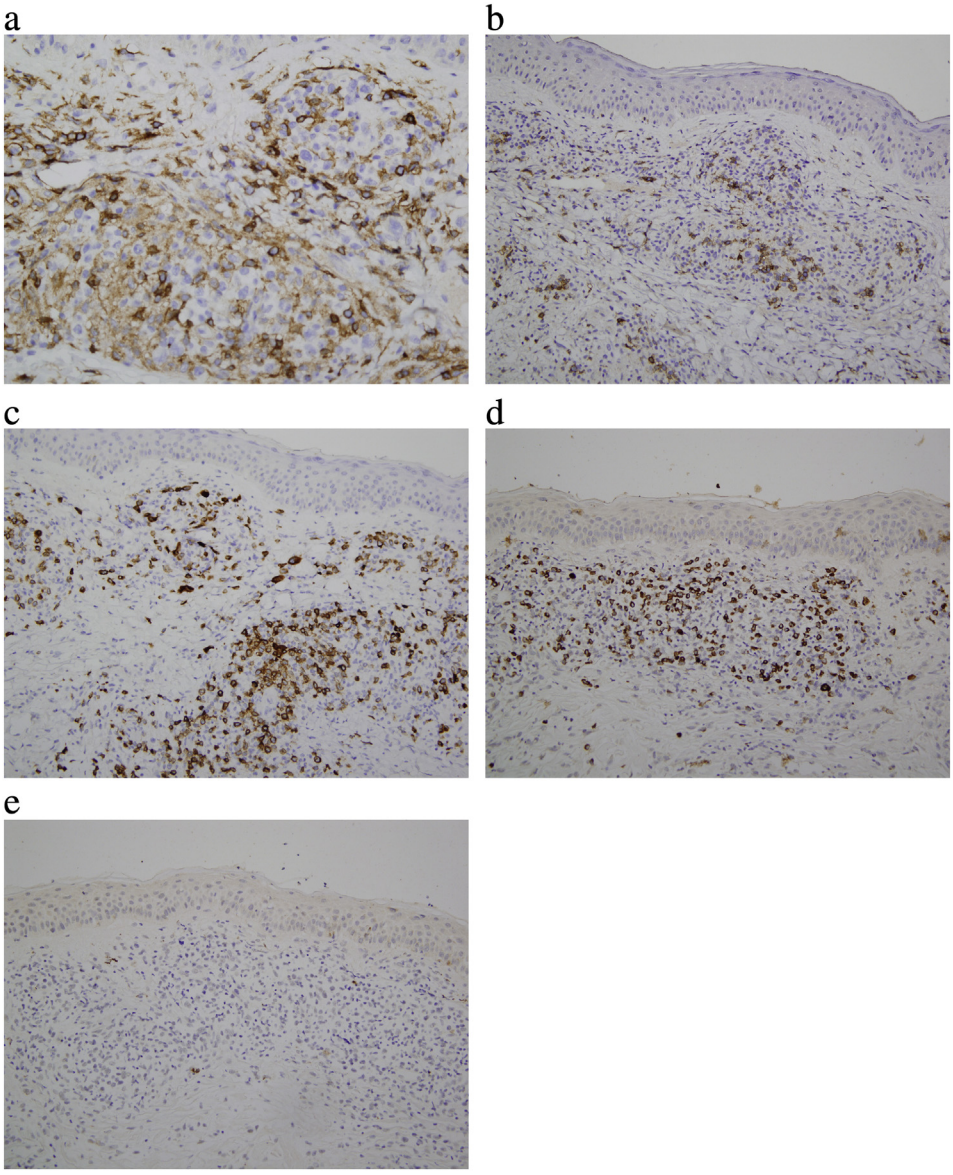

Fig. 13. There is significant staining of the infiltrate for CD4. The CD4 preparation highlights histiocytes whereby there is weak cytoplasmic staining. There is a more intense pattern of immunoreactivity within the CD4 T cells (13a). A number of the CD4+ T cells express PD1 (13b). The dominant infiltrate in fact is of B cell lineage as revealed by the extent of immunoreactivity for CD79a (13c). There is clear-cut kappa light chain restriction (13d). The lambda stain is essentially negative (13e) (case 8).

Table 4
Molecular clonality studies.

Case	T cell	B cell
(1)	Monoclonal	Polyclonal
(2)	Not performed	Not performed
(3)	Not performed	Not performed
(4)	Not performed	Not performed
(5)	Monoclonal	Monoclonal
(6)	Monoclonal	Not performed
(7)	Not performed	Not performed
(8)	Monoclonal	Polyclonal
(8)	Monoclonal	Polyclonal
(8)	Monoclonal	Polyclonal
(8)	Polyclonal	Polyclonal
(9)	Monoclonal	Polyclonal
(10)	Not performed	Not performed
(11)	Monoclonal	Polyclonal

but not in every case. Suarez and co-workers reported a patient with AITL who developed skin lesions that exhibited a monotypic plasma cell infiltrate accompanied by scattered larger atypical B cells [35]. In 2009, Bayerl and co-workers presented a 66-year-old male with a 1-year history of fatigue; he had a mild pancytopenia. He developed a plaque that was biopsied and initially interpreted as a lambda light restricted marginal zone lymphoma. He later developed lymphadenopathy whereby there was biopsy proven nodal diffuse large cell B cell lymphoma and AITL. During the course of his illness he developed other plaques with significant degree of B cell infiltration and evidence of light chain restricted plasma cell infiltrates that manifested isotype switching. He ultimately died of a diffuse large cell B cell lymphoma exhibiting kappa light chain restriction. All of these cases emphasize that clonal B cell proliferations independent of EBV infection occur in follicular helper T cell lymphoma and does not imply a neoplastic B cell event especially in the setting of AITL.

Few clinical studies have examined the prognostic significance of B-cell expansion in AIL, but it would appear that at least clonality

documented via IgH heavy chain gene rearrangements does not appear to be a significant prognosticator in the realm of AITL.

In all of the cases presented in this series, a critical differential diagnostic consideration was T cell rich marginal zone b-cell lymphoma. The main features that were not supportive of this diagnosis were the extent of T cells cytologic atypia, the abnormal phenotypic profile as characterized by the extent of follicular helper T cell infiltration and the lack of germinal centers. In cases where the plasma cells appeared somewhat atypical, an evolving low-grade B cell lymphoproliferative disorder had to be considered although all cases excluding one showed a polyclonal B-cell molecular profile. In one case the degree of immunoblastic B cell infiltration and plasma cell atypia could have suggested a diagnosis of a blastic marginal zone lymphoma. Ultimately it was concluded that the infiltrates were more likely reactive clonal expansions of post germinal B cells in the setting of the follicular helper T cell milieu.

There are indeterminate clonally restricted plasma cell infiltrates that can be observed in other settings such as pseudolymphoma. We recognize lymphomagenesis as a multistep process and therefore seeing emerging clonally restricted T or B cell infiltrates in a pseudolymphomatous process could define a progressive step toward lymphoma. One of our cases of AITL (case 9) developed an EBV positive diffuse large cell B cell lymphoma that was lambda light chain restricted. Lambda light chain restriction was noted in an earlier biopsy. It is possible that EBV infection of the clonally restricted B cells in the setting of combined iatrogenic and endogenous immune dysregulation may have eventuated into a lymphoma providing a potential link between the development of clonally restricted plasmacytic infiltrates and the evolution to a frank lymphoma. One study showed that the initiation of EBV replication occurred in cells that had the phenotype of plasma cells while it was not detected in B cells that were either germinal center B cells or naïve B cells. The plasma cells replicating the virus are produced through terminal differentiation of a small pool of post germinal B cells including those that exhibit latent infection [36].

The basis of clonal plasma cell expansion independent of EBV infection likely relates to the B cell promotional effect by neoplastic follicular helper T cell population. In the normal germinal center counterpart the maturation and clonal expansion with somatic hypermutation and class switching is attributable to the interaction of the follicular helper T cells with the germinal center via surface molecules and certain cytokines such as IL-21. The net result of the interaction is the production of memory B cells and antibody producing plasma cells. Under neoplastic conditions where the follicular helper T cell population is excessive an even more robust B cell expansion would occur and hence result in emerging clonally restricted B cells. Conversely, studies have shown that plasma cells, which have undergone isotype switching express major histocompatibility complex class II antigens and exhibit other costimulatory molecules critical for antigen presentation result in the induction of helper T cell function. However these antigen primed plasma cells decreased molecules associated with the follicular helper T cell phenotype such as BCL6 or IL21 emphasizing a negative feedback loop. It may be that the plasma cell accumulation is therefore part of a counterregulatory response [37].

In conclusion, monoclonal plasmacytic proliferations occur in the setting of primary cutaneous follicular helper T cell lymphoma and is reflective of the critical role of follicular helper T cells in promoting and driving B cell proliferation and terminal memory B cell and plasma cell differentiation. Even in cases showing a very extensive degree of B cell infiltration these infiltrates do not necessarily denote ensuing B cell lymphoma. While clonality is an important and critical step in lymphogenesis it does not translate into oncogenesis. Plasma cell atypia and or accumulation of transformed blastic clonally restricted B cells can be seen and do not define the morphologic sine que none of a malignant transformation. It is hard to establish precisely the significance of these infiltrates. While the clinical course does not appear to be significantly different compared to those cases where these clonally restricted plasma cell infiltrates are not seen there are cases where these clonal infiltrates presage the development of diffuse large cell B cell lymphoma.

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