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Original Contribution

Post-thymic CD4 positive cytotoxic T cell infiltrates of the skin: A clinical and histomorphologic spectrum of the unique CD4 positive T cell of immunosenescence

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ABSTRACT

T cell lymphoproliferative disorders that arise in the skin are mainly derived from post thymic T cells most commonly of CD4 subset. Human CD4 positive T cells are dynamic exhibiting phenotypic and functional malleability. For example, with repetitive antigen exposure most commonly associated with age, CD4 positive T cells acquire a cytotoxic phenotype. The authors present four cases characterized by cutaneous infiltrates of cytotoxic CD30 negative CD4 positive T cells in the skin; three cases were forms of malignant lymphoma other than mycosis fungoides and one case was a reactive lymphomatoid photodermatosis associated with underlying collagen vascular disease. The three patients with lymphoma were adult men, two above 50 years of age and all with disseminated cutaneous disease. One of these patients whose biopsy showed a large cell morphology succumbed to the disease while one patient with localized disease responded to local radiation. In all three cases there was a nodular and diffuse pan-dermal infiltrate which was predominated by non-cerebriform atypical lymphocytes ranging from small to intermediate sized cells in two cases to a large cell dominant morphology in one case. The biopsies showed some degree of epidermotropism, and in one case it was striking. Neoplastic cells were positive for CD4, and at least one cytotoxic protein (i.e. granzyme and/or TIA). CD56, CD57 or CD30 were negative. In addition, CD28, the naïve T cell marker, was negative. Based on the few cases reported herein, one might suggest that the prognosis mirrors that seen in other forms of cutaneous T cell lymphoma with mature small cell dominant infiltrates exhibiting an indolent pattern while a CD30 negative large cell T cell lymphoma would be expected to demonstrate an aggressive clinical course.

1. Introduction

The majority of cutaneous T cell lymphomas represent either mycosis fungoides (MF) or primary cutaneous CD30 positive lymphoproliferative disorders (LPD) either in the context of anaplastic large cell lymphoma (ALCL) or lymphomatoid papulosis (LYP). The remainder comprises rare forms of cutaneous lymphoma, which cumulatively represent less than 5% of all cutaneous lymphomas. These less common variants of cutaneous T cell lymphoma encompass a broad clinical and morphologic spectrum ranging from certain low grade lymphoid neoplasms that have now been recategorized as lymphoproliferative disorders such as so called primary cutaneous CD4+ small/medium sized pleomorphic T cell LPD and CD8+ indolent lymphoid proliferation of the face and acral sites to those lymphomas that exhibit an aggressive clinical course. This latter category includes primary cutaneous gamma delta T cell lymphoma, CD30 negative large cell T cell lymphoma, primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma, and NK-T cell lymphoma [1-3]. The therapeutic approaches are as varied as the nosologic classification ranging from topical therapy for early stage MF to aggressive ablative chemotherapy with stem cell transplantation in certain forms of aggressive peripheral T cell lymphoma [4].

From an ontogeny perspective, the majority of T cell lymphoproliferative diseases that involve the skin are derived from post thymic T cells and include Th1 or Th2 CD4 positive T cells, follicular helper T cells, gamma delta T cells, and NK-T cells. Persistent states of antigen stimulation and immune dysregulation that is either iatrogenic or endogenous in nature define factors in the development of cutaneous lymphoma, reflective of the multistep process of lymphomagenesis.

T cells exhibit a dynamic phenotype and function that evolves with

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age, attributable to the repetitive antigenic exposure that occurs through life. A pathological acceleration of immunosenescence occurs in the setting of autoimmune diseases or chronic viral infections due to the extent of adaptive immune responses triggered by response provoking antigens. Each effective immune response to the cognate antigen induces progressive cell differentiation with resultant restriction of the T cell repertoire and ultimately cell cycle arrest. The latter is attributable to critical telomere length reduction inducing a state of replicative senescence. Although these T cells are senescent, they acquire new functional capabilities such as the expression of cytotoxic proteins [5-7].

Herein, we describe four cases of cutaneous infiltration of the skin showing a distinctive CD30− CD4+ cytotoxic T cell infiltrate including three cases that were diagnostic of a peripheral T cell lymphoma; we postulate that the implicated T cell is one reflective of a state of immunosenescence.

2. Materials and methods

Four cases were encountered in the dermatopathology practice of one of the authors (CMM). In each case light microscopic studies along with comprehensive phenotypic analysis and molecular studies were conducted to ascertain the nature of the lymphocytic infiltrate as part of the routine diagnostic work up of the case. In all cases the dominant infiltrate was a CD4 positive cytotoxic T cell lacking in CD30 expression. In each case the following immunohistochemical stains were performed: CD2, CD3, CD5, CD7, CD16, CD56, CD57, Beta F1, TIA, perforin, and CD30. In addition, three of the four cases were stained with CD28 (1:100 dilution, rabbit polyclonal antibody, Biorbyt).

With respect to the molecular studies, T cell receptor gene rearrangement studies were conducted. Cells were procured from the specimens, lysed, and DNA was extracted. The BIOMED2 assays were used to assess for the presence of T cell receptor gamma chain gene rearrangements. Two multiplex PCR reactions were conducted using two sets of primers in each reaction that was hybridized to the V and J regions of the T cell receptor gamma gene.

3. Results

3.1. Case 1

The patient was a 79-year-old female who presented in 2008 with a three-month history of fixed tender plaques on the scalp, periorbital, cervical, and auricular areas initially unresponsive to topical measures and antihistamines. The patient also had a history of rheumatoid arthritis. A biopsy was performed of the chin and additional tissue was procured from the right shoulder area that was submitted for direct immunofluorescent testing. The patient was seen by hematology-oncology service at which point the cutaneous lesions, however, had resolved spontaneously; the patient died in 2017 at the age of 92 from natural causes unrelated to lymphoproliferative disease.

3.1.1. Light microscopic findings

The biopsy showed a significantly atypical lymphohistiocytic infiltrate that was found in close apposition to vessels and nerves and frankly permeative of those structures, defining both a lymphomatoid vasculopathy and neuritis. A grenz zone separated the infiltrate from the overlying epidermis. The neurotropism of the infiltrate was particularly conspicuous with disruption of the perineurium and permeation of the endoneurium by the aforesaid atypical mononuclear cell populace (Fig. 1a). The lymphoid elements were pleomorphic comprising small, intermediate and larger lymphoid forms (Fig. 1b, c); the cells exhibited an open nuclear chromatin with nuclear contour irregularity although without cerebriform nuclear outlines. A significant interface dermatitis or increase in mesenchymal mucin was not present.

3.1.2. Phenotypic studies

There was a significant predominance of CD4 to CD8 with the infiltrate almost being exclusively CD4 positive (Fig. 1d, e). Reduction in CD7 expression was noted compared to CD2 in the realm of 60% and the infiltrate was predominantly negative for CD62L. A very striking feature of the infiltrate was the marked granzyme expression throughout the infiltrate far exceeding the number of CD8 positive cells indicative that the CD4 positive T cells in fact showed cytotoxic protein expression (Fig. 1f). About 20% of the infiltrate was CD56 positive. Only rare cells were positive for CD30. A few CD20 positive B cells were noted. Immunohistochemical staining for CD28 was negative. Special stains including Steiner, acid fast, and Fite acid fast stains, were negative for microbial pathogens.

3.1.3. Direct immunofluorescent studies

Direct immunofluorescent studies showed a striking granular deposition pattern for IgM along the dermal-epidermal junction with a similar significant staining pattern noted for C3d and C4d. Of interest was the lack of immunoreactivity for IgG and IgA and only minimal staining for C5b-9 along the dermal-epidermal junction. A diagnosis was rendered of a positive lupus band test of IgM isotype recognizing that this variant of the positive lupus band test can be non-specific.

3.1.4. Molecular studies

Molecular studies demonstrated a polyclonal result.

3.2. Case 2

The patient was a 75-year-old male who underwent a left total knee replacement in January 2016. Subsequently, he developed multiple lesions throughout his legs, most notably the left anterior thigh area, which was clinically thought to be cellulitis and treated with antibiotics and steroids without any significant improvement. The patient was then seen by a dermatologist in July 2016 whereby the biopsy was interpreted as being an injection site reaction. In November 2016 a repeat biopsy showed a mononuclear cell infiltrate with occasional granulomas that was thought to be reactive but a suspicion of lymphoma was subsequently raised when molecular studies demonstrated a T cell clonal gene rearrangement. He presented to the hematology/oncology division in December 2016 with a localized nodule of roughly 7 × 7 cm on the left anterior thigh (Fig. 2a). His physical examination was otherwise unremarkable. A biopsy was performed and a diagnosis of lymphoma was rendered as detailed below. A PET/CT in January 2017 revealed enhancement in the anterior left thigh as well as left pelvic and inguinal lymph nodes; however, a subsequent pelvic lymph node biopsy was negative for lymphoma. A bone marrow biopsy was also negative. The patient received local radiation to the left thigh (4500 cGy, 25 fractions), which was complicated by radiation cellulitis that resolved with 3 weeks oral antibiotics therapy. The patient was disease free over the next year of follow-up.

3.2.1. Light microscopic findings

The biopsy from the anterior thigh showed an extensive diffuse lymphocytic infiltrate, spanning the entire dermis with accentuation around adnexal structures and marked infiltration of the adventitial dermis of the eccrine coil. Some degree of epidermotropism was also noted (Fig. 2b). The infiltrate was predominantly composed of small lymphocytes without any evidence of large cell transformation. An interesting feature was also the admixture of multinucleated histiocytes with a ring-like arrangement of nuclei and emperipolesis of lymphocytes, which were found within the peripheral aspect of histiocyte cytoplasm resulting in a somewhat scalloped cytoplasmic contour (Fig. 2c). In examining the infiltrate under oil the cells had a non-cerebriform atypical appearance whereby the chromatin was finely dispersed with prominent nuclear membranes and conspicuous basophilic nucleoli (Fig. 2d).

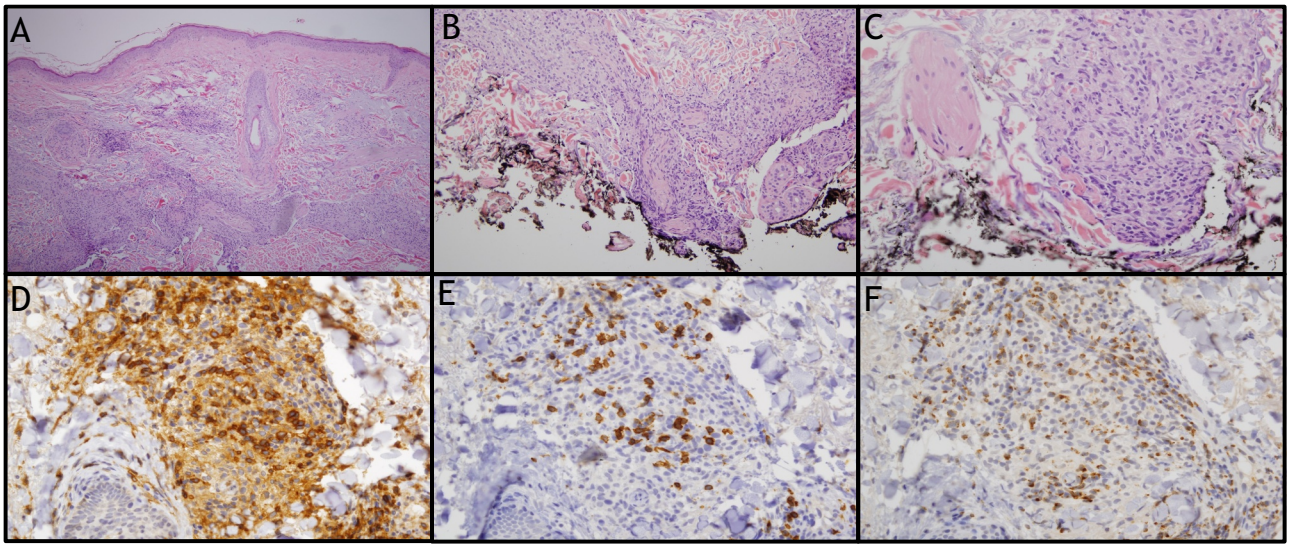

Fig. 1. a, b: The biopsy showed a significantly atypical lymphohistiocytic infiltrate that was found in close apposition to vessels and nerves and frankly permeative of those structures, defining both a lymphomatoid vasculopathy and neuritis (H&E, 4×(a), 20×(b)).
c: The lymphoid elements were pleomorphic comprising small, intermediate and larger lymphoid forms; the cells exhibited an open nuclear chromatin with nuclear contour irregularity albeit none had cerebriform nuclear outlines (H&E, 40×).
d, e: The CD4 (panel d) to CD8 (panel e) ratio was very high with the infiltrate almost being exclusively CD4 positive.
f: A very striking feature of the infiltrate was the marked granzyme staining throughout the infiltrate far exceeding the number of CD8 positive cells indicative that the CD4 T cells in fact showed cytotoxic protein expression.

3.2.2. Phenotypic studies

There was extensive expression of pan T cell marker CD3 while the B cell component was quite minimal. The infiltrate was composed almost exclusively of CD4 positive T cells (Fig. 2e) with only a few reactive CD8 positive lymphocytes (Fig. 2f). Extensive expression of granzyme (Fig. 2g) and TIA (Fig. 2h) was noted among T cells. A marked reduction in the expression of CD7 likely in the realm of 80% was present while CD5 was mostly preserved. PD-1, CD10 and EBER were negative and significant immunoreactivity was not observed for CD56, CD163, CD11c, and CD30. Immunohistochemical staining for CD28 was also negative.

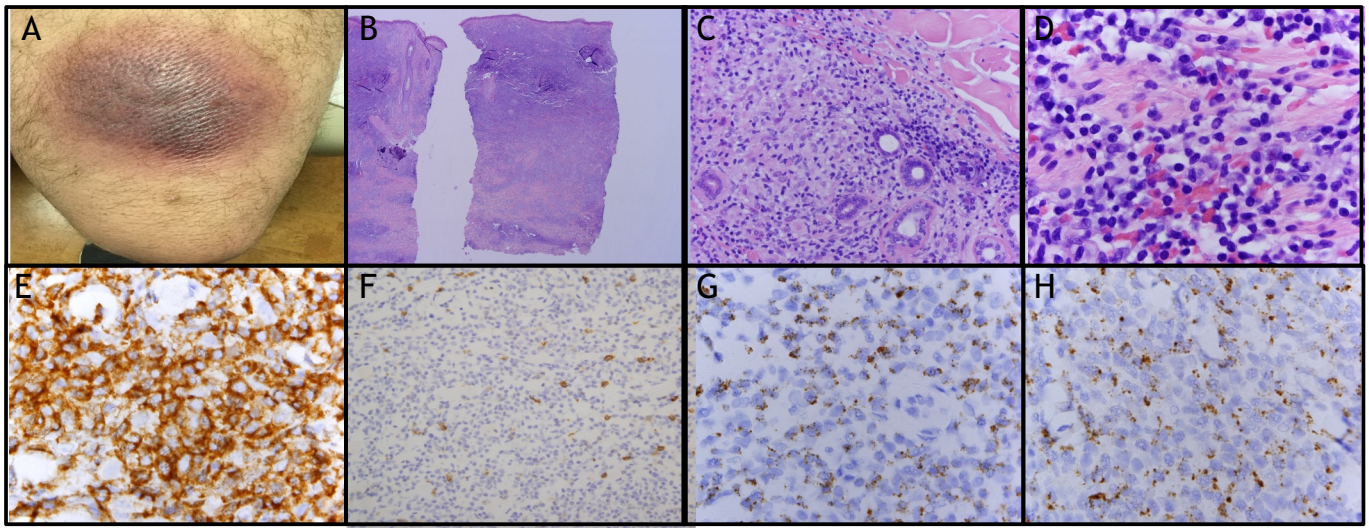

Fig. 2. a: The patient had a 7 cm violaceous nodule involving the anterior left thigh.
b: The infiltrate spanned the entire sampled thickness of the dermis with close apposition to adnexal structures and marked infiltration of the adventitial dermis of the eccrine coil. There was also some degree of epidermotropism (H&E, 2×).
c: An interesting feature of the infiltrate was the admixture of multinucleated histiocytes exhibiting a ring-like arrangement of nuclei with some emperipolesis of lymphocytes. The lymphocytes were found within the cytoplasms at the periphery of the histiocyte resulting in a somewhat scalloped cytoplasmic contour (H&E, 40×).
d: Cytomorphologically the infiltrate was predominantly a small lymphocytic one without any evidence of large cell transformation. In examining the infiltrate under oil the cells had a non-cerebriform atypical appearance whereby the chromatin was finely dispersed with prominent nuclear membranes and conspicuous basophilic nucleoli (H&E, 100×).
e, f: The infiltrate was composed almost exclusively of CD4 positive T cells (panel e) with only a few reactive CD8 positive T lymphocytes (panel f).
g, h: The cells were extensively positive for granzyme (panel g) and TIA (panel h). Significant immunoreactivity was not observed for CD56, CD163, CD11c, and CD30.

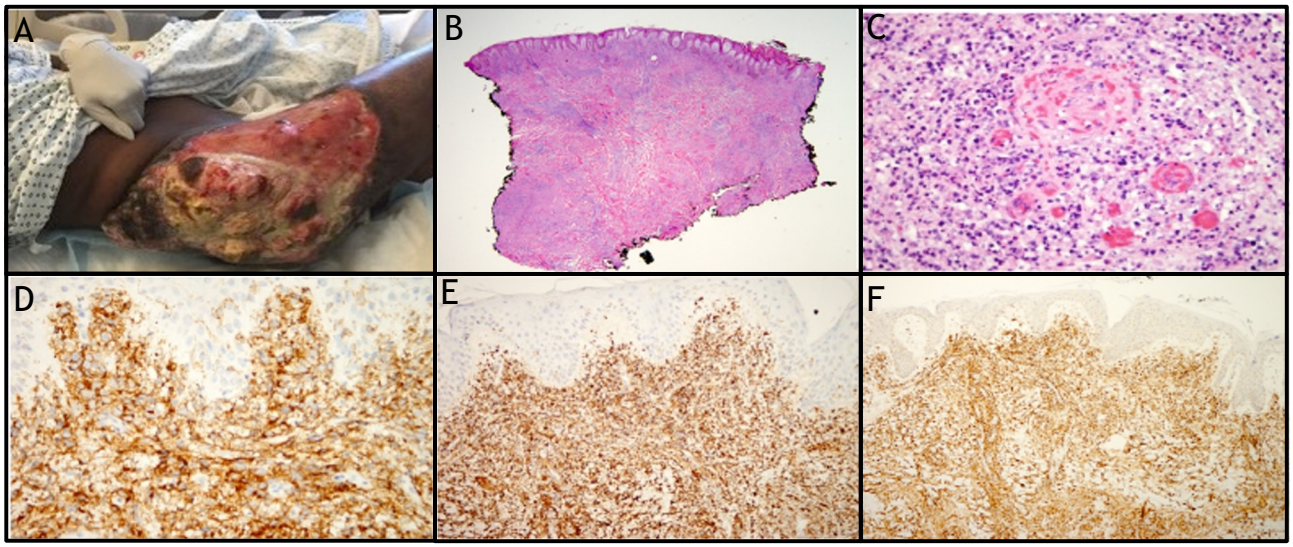

Fig. 3. a: The patient was a 21-year-old male who presented in June 2013 with a large fungating cutaneous tumor of the right hip area.
b: All of the biopsies of the skin procured in this patient showed the same fundamental process with a highly atypical mononuclear cell infiltrate involving the entire sampled thickness of the dermis with striking cellular necrosis (H&E, 2×).
c: The infiltrate had a proclivity to surround and invade blood vessels with attendant angiodestruction (H&E, 40×).
d: The cells were CD4 positive but without staining for CD8.
e, f: There was extensive immunoreactivity for granzyme (panel e) and TIA (panel f).

3.2.3. Molecular studies

Molecular studies demonstrated T cell clonality exhibiting weak clonal peaks at 223 base pairs and 172 base pairs in a polyclonal background.

3.3. Case 3

The patient was a 21-year-old male who presented in June 2013 with a large fungating cutaneous tumor of the right hip area (Fig. 3a). After a diagnosis of T cell lymphoma was rendered the patient was admitted from December 2014 through May 2015 for multi-agent chemotherapy with etoposide, prednisone, vincristine (Oncovin), cyclophosphamide, and doxorubicin hydrochloride (hydroxydaunorubicin hydrochloride) (EPOCH) after which he was discharged, and then lost to follow up. He later presented to the hospital in December 2014 when imaging studies showed a large mass involving the skin and subcutaneous tissue with extension into the muscles of the right hip and thigh area. There was also concomitant cervical, thoracic, and abdominal lymphadenopathy with multiple hepatic and intrapulmonary lesions. After the diagnosis of recurrent T cell lymphoma was made he received EPOCH for a total of 6 cycles, which were completed in May 2015. Since his discharge in May 2015 he had not returned to the oncology clinic until November 2015 when he presented with a large calcified mass in the right flank area measuring 26 cm in greatest dimension. There was also involvement of the sacroiliac joint, multiple hepatic lesions and extensive abdominal and pelvic lymphadenopathy. At that point in time the repeat skin biopsy confirmed the diagnosis of persistent T cell lymphoma. The patient was given romidepsin and palliative radiation before he passed away in February 2016.

3.3.1. Light microscopy

All of the biopsies of the skin procured in this patient showed the same fundamental process of a highly atypical mononuclear cell infiltrate involving the entire sampled thickness of the dermis with striking cellular necrosis (Fig. 3b). The infiltrate was found in close apposition to the epidermis with only very focal areas of epidermotropism. There were some supervening eczematoid alterations. The malignant cells distended the dermal papillae, which also showed a vacuous edematous alteration. The infiltrate had a proclivity to surround and invade blood vessels with attendant angiodestruction (Fig. 3c). There was significant mural and luminal fibrin deposition as well as occlusion of the vascular lumina by necrotic tumor cells admixed with fibrin. The cells that defined the majority of the infiltrate were large lymphocytes, about 15 μm in size, with a monomorphic blastic morphology, finely dispersed chromatin, round to oval nuclei and small basophilic nucleoli. A striking pattern of pseudoepitheliomatous hyperplasia was also present in the vicinity of the ulcer.

3.3.2. Phenotypic studies

The tumor cells were highlighted by pan T cell markers CD2 and CD5, although the CD3 and CD7 stains were essentially negative. The cells were CD4 positive (Fig. 3d), without staining for CD8. There was extensive expression of granzyme (Fig. 3e) and TIA (Fig. 3f). Significant immunoreactivity for CD16, C30, CD56, CD57, and EBER was not identified. There was also no significant staining for CD123, CD14, FoxP3, MXA, or TCL1 oncogene. CD28 immunohistochemical stain was also negative.

3.3.3. Molecular studies

Molecular analysis revealed monoclonality.

3.4. Case 4

The patient was a 60-year-old male with a past medical history of left tonsillar squamous cell carcinoma (diagnosed in 2016, treated with radiation and chemotherapy) who presented to the dermatologist with a 10 × 6 cm raised erythematous to violaceous nodule on the right forearm of a few weeks duration (Fig. 4a). In addition, clinical examination demonstrated a widespread erythematous scaly rash that had been present for seven weeks. The clinical impression was that this background diffuse rash had the appearance of MF although at variance with classic MF was the fairly sudden onset (Fig. 4b). Biopsies were performed of both the large exophytic nodule on the right forearm as well as the mycosis fungoides-like rash. Peripheral blood flow cytometry and a PET/CT were performed and were negative. A wide local excision of the right forearm nodule was performed in December 2017 with subsequent skin flap repair. During a visit to his oncologist's office

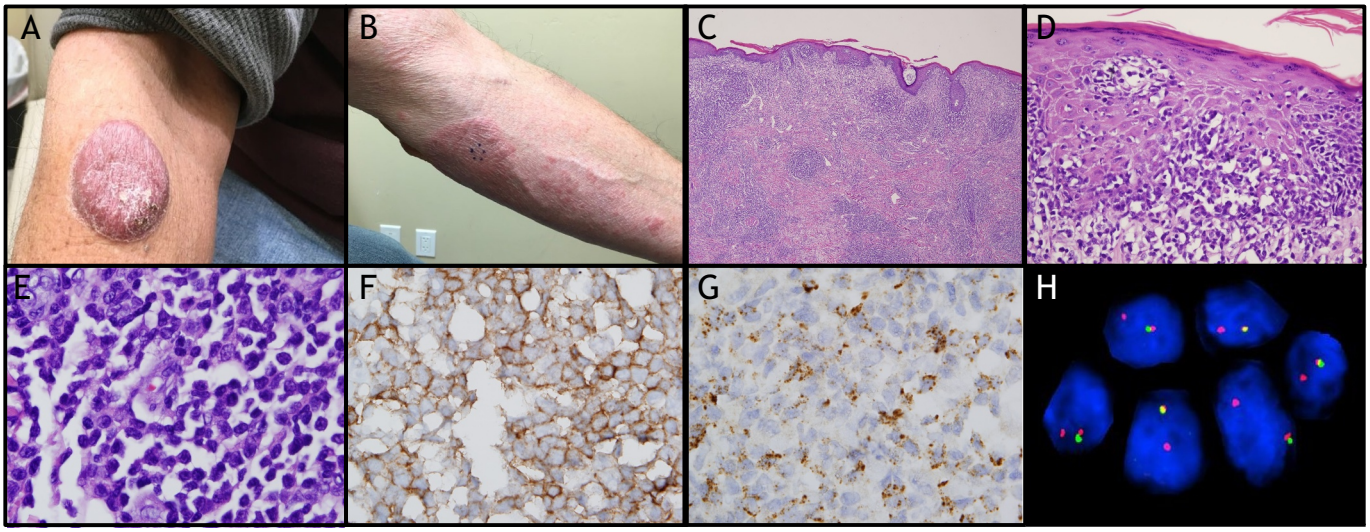

Fig. 4. a: Case #4 was a 60-year-old male who presented to the dermatologist with a 10 × 6 cm raised erythematous to violaceous nodule on the right forearm of a few weeks duration.
b: In addition, there was a more widespread erythematous scaly rash that had been present for seven weeks. While the diffuse rash made a clinical impression of mycosis fungoides (MF), at variance with classic MF was the sudden onset.
c: Common to both biopsies was significant epidermotropism of atypical lymphocytes defining a pattern closely recapitulated MF. The epidermotropic component was quite striking with large coalescing aggregates of atypical lymphocytes within the epidermis simulating a Pautrier's microabscess but without the typical cerebriform cytology that defines classic MF (H&E, 4×).
d: In addition, the tumor nodule showed a nodular and diffuse infiltrate exhibiting variable epidermotropism and adnexotropism predominated by smaller lymphocytes with only a minor larger cell component (H&E, 40×).
e: Cytomorphologically, there was monomorphism whereby the cells demonstrated a less condensed chromatin and more rounded nuclear contours with conspicuous nucleoli without the typical cerebriform atypia of MF (H&E, 100×).
f: The infiltrate is highlighted by CD4 without any staining for CD8. While there was no loss of CD7, the atypical lymphocytes were mostly negative for CD5.
g: There is extensive staining of the atypical cells for PD1 and TIA while the granzyme preparation is negative.
h: A C-MYC rearrangement with 3′MYC deletion (loss of green signal) was seen in 80% of the cells by fluorescence in situ hybridization (FISH). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in February 2018, worsening plaque-like lesions were noted over his bilateral shins (left > right) in addition to stable plaques over the anterior abdomen and left deltoid area. Given the widespread nature of the lesions, he required systemic therapy and was referred to another center for more advanced care. He underwent 6 cycles of CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) which led to complete regression of his skin rash. Within 4 weeks of his last dose his rash has returned. He is now scheduled for ablative chemotherapy and a stem cell transplant. Staging work up including bone marrow biopsy does not reveal any evidence of extracutaneous disease to date. Apart from symptomatic cutaneous disease he feels relatively well although he does report fever and night sweats.

3.4.1. Light microscopic findings

Common to both biopsies was significant epidermotropism of atypical lymphocytes defining a pattern that closely recapitulated mycosis fungoides (Fig. 4c). The epidermotropic component was quite striking whereby there were large coalescing aggregates of atypical lymphocytes within the epidermis simulating Pautrier's microabscesses although without the typical cerebriform cytology that defines classic atypical lymphocytes of MF. In addition, the exophytic lesion showed a striking nodular and diffuse infiltrate exhibiting variable epidermotropism and adnexotropism predominated by smaller lymphocytes with only a minor larger cell component (Fig. 4d). The lymphocytes while atypical, showed an element of monomorphism whereby the cells demonstrated a less condensed chromatin and more rounded nuclear contours with conspicuous nucleoli, although once again without the typical cerebriform atypia of MF (Fig. 4e). A significant degree of histiocytic infiltration was also present to the point of imparting a granulomatous quality to the infiltrate.

3.4.2. Phenotypic studies

The lymphocytes were positive for CD4 (Fig. 4f) without any staining for CD8. While there was loss of CD5, significant reduction in CD7 expression was not seen. There was extensive staining of the atypical cells for PD1 and TIA (Fig. 4g) although the granzyme preparation was negative. CD56, CD7 and CD30 were negative. Cytogenetic studies were also performed which showed a C-MYC rearrangement with 3′MYC deletion in 80% of the cells by fluorescence in situ hybridization (FISH) (Fig. 4h).

4. Discussion

We have presented four patients (21, 60, 75, and 79 years of age) who developed atypical T cell infiltrates of the skin with a varied clinical and histomorphologic presentation. The uniqueness of the cases rests in the nature of the implicated T cell, being a mature cytotoxic CD4 positive T cell. The cytotoxic features were revealed by significant cytotoxic protein expression as revealed by the degree of staining for TIA in all 4 cases and granzyme in three of the cases. In three of the cases the findings were diagnostic of peripheral T cell lymphoma. In one case, while the light microscopic and phenotypic findings were suggestive of peripheral T cell lymphoma, the patient's subsequent clinical course was more in keeping with a reactive process.

A synoptic review of these cases will be given. In Case 1 the process presented in a photodistributed fashion in a 79-year-old woman; while the infiltrate was atypical, it was non-effacing with polyclonal molecular studies. The disease eventually resolved spontaneously and the patient passed away years later of unrelated causes. In Cases 2, 3, and 4 diagnostic features of a T cell lymphoma were uncovered whereby in Case 2, the neoplastic process represented a CD30 negative large cell T cell lymphoma while in the other two cases the processes were

predominated by small monomorphic T cells. In Case 3 where the infiltrate was dominated by large neoplastic T cells, the patient's clinical course was subsequently aggressive as manifested by widespread metastatic disease to the liver, spleen, and lymph nodes. In contrast, the patients with the small lymphocytic form of lymphoma are alive with one patient (Case 2) in remission following local radiation and Case 4 with widespread cutaneous disease that initially responded to chemotherapy but has since recurred without any evidence of extracutaneous disease. The aggressive course of the CD30 negative large cell T cell lymphoma case is similar to the aggressive clinical course seen in the other forms of primary cutaneous CD30 negative peripheral T cell lymphoma, manifesting a large transformed morphology [8,9]. Case 4 was particularly interesting because of its resemblance clinically and light microscopically to MF. However, the onset was quite sudden with a rapid course to tumor progression while cytologically the cells were atypical but not cerebriform.

When one considers commonality in morphology for the three cases of T cell lymphoma, it is in the context of an extensive diffuse and nodular dermal-based infiltrate. The infiltrates could be accentuated around nerves and blood vessels and in the one case associated with patient demise, there was a significant angiodestruction. The extent of histiocytic infiltration imparted a granulomatous quality to the infiltrate. A significant epitheliotropic component was identified in all three cases with lymphoma either in the context of epidermotropism and or folliculotropism. Adventitial dermal involvement was also common. In one case, the pattern was most reminiscent of MF with prominent epidermotropism forming intraepidermal collections that closely simulated Pautrier's microabscesses. Cytomorphologically, the prevailing cell type was noncerebriform and ranged from being a small cell dominant infiltrate to a large transformed blastic morphology. As discussed above, the cytomorphology was a critical factor in determining clinical outcome.

The uniqueness of all of the cases is the nature of the CD4 positive T cells that defined the dominant infiltrate. Although cytotoxic protein expression was seen in all cases, positive staining for CD56, CD16 or CD57 characteristic of NK-T cell lymphoma was not seen. Cytotoxicity is either attributable to granule exocytosis or reflective of the interaction of FAS and FAS ligand. Perforin induces pores into a cell resulting in osmotic lysis. TIA (GMP-17) is a granule protein that is mostly restricted to NK cells, neutrophils and CD8 positive T lymphocytes. TIA is expressed by such cells regardless of their activation status. Perforin and granzyme are inducible when the cells are in a state of activation and this would correlate with the induction of cytolytic activity [10]. Not surprisingly in the case where an aggressive clinical course developed, the cytotoxic cells expressed both granzyme and TIA. There are really no reports to date on cutaneous lymphomas that are derived from CD4 positive cytotoxic T cells that are CD30 negative other than cases of tumor stage MF and a subset of cases that fall under the rubric of small cell variant of ALCL [11].

Lymphomagenesis is a multistep process that likely has as its inception an overzealous clonal response in a benign counterpart. In this regard, the classification of lymphoma is one that may be reflective of the ontogeny of the benign counterpart. The natural age-related deterioration of the lymphocyte compartment is heralded by the accumulation of mature T cells that express CD4 that have lost their expression of CD28, falling under the designation of a CD4 positive/CD28 null T cell. CD28 is a homodimeric stimulatory cell surface receptor of the Ig superfamily. It is expressed on virtually all T cells in rodents. In humans it is largely limited in expression to CD4 positive T cells and only half of CD8 positive T cells. CD80 and CD86 are the natural ligands for CD28. If they are upregulated by an exogenous trigger, the end result would be T cell proliferation. CD28 induces a co-stimulatory signal in T cells recognizing cognate antigen major histocompatibility complexes in their T cell receptor [12]. It should be emphasized that CD28 exerts a critical influence on T cell survival. It is a booster to T cell proliferation. The interaction between CD28 and CD80 leads to the intracellular accumulation of the antiapoptotic protein BCL-XL rendering T cells resistant to intrinsic and extrinsic death signals [12]. The premature accumulation of an immunosenescent T cell that no longer expresses the critical CD28 molecule has been described in patients with various autoimmune conditions including lupus erythematosus, rheumatoid arthritis and multiple sclerosis as well as patients who have underlying cardiovascular disease [13,14]. These T cells secrete inflammatory mediators and cytolytic molecules and hence, not surprisingly, one of the cardinal hallmarks of this T cell population is the expression of cytotoxic proteins such as granzyme and TIA. The chronic proinflammatory environment, repeated immune stimulation in autoimmune disease, certain viral infections and repetitive inflammatory events that occur with age can result in aging of the immune system either in the context of chronological normal aging or accelerated aging in the setting of autoimmune and viral disease. When there is an acceleration of aging of the immune system, it falls under the designation of *premature immunosenescence* [6,7]. At least in the setting of cardiovascular diseases, this immunosenescent T cell population can migrate to the sites of atherosclerotic change, destabilizing the atherosclerotic plaque, leading to cardiac events. Paradoxically, lymphocytes that express cytotoxic proteins do not specifically undergo apoptosis due to various mechanisms including intracytoplasmic inhibitors of serine proteases namely serpins and a cell surface protective molecule that prevents the disruption of the cytoplasmic membrane by perforins [15].

It may seem counterintuitive that a lymphocyte which is unable to proliferate could have neoplastic potential since the very definition of neoplasia is one of autonomous clonal expansion of a cell. The lack of co-stimulatory molecules CD27 and CD28 can potentially be overcome by activating NK cell receptors such as NKG2D with its specific ligand, defining a venue for proliferation in a cell that is otherwise not designed for cellular propagation [16]. Another potential manner in which T cell proliferation can occur is one of interleukin (IL)-15 release from the monocytes. $CD4^+$ $CD28^{null}$ T cells do not proliferate in response to allogeneic stimulation, unless IL-15 is added. However, the additional IL-15 increases the frequency of proliferating alloreactive T cells to 30.5% without inducing CD28 expression [17].

As a point of reiteration, the literature precedent on CD4 + T cell lymphomas of the skin exhibiting cytotoxic properties is limited to endogenous CD30 positive LPDs represented by ALCL, LyP and tumor stage MF with large cell transformation. When one considers cytotoxic granule expression in the benign lymphocyte counterpart, the classic cell types are natural killer cells, double negative gamma delta T cells and cytotoxic CD8 positive T cells. The cytotoxic molecules include the specific proteases granzyme A and B and T cell restricted intracellular antigen. Each of the cytotoxic proteins plays an important role leading to cell death. Perforin for example elicits disruption of the integrity of the cytoplasmic membrane while granzyme results in the initiation of cellular apoptosis through the activation of caspases. The critical role of these cytotoxic granules is in the context of immunosurveillance killing of tumor cells and exogenous pathogens [15,18].

The delivery of cytotoxic proteins to target cells enables neoplastic cells to induce apoptosis/cell death of critical immunosurveillance antitumor cells, hence facilitating tumor progression. Paradoxically, lymphocytes that express these cytotoxic proteins do not specifically undergo apoptosis due to various protective mechanisms including intracytoplasmic inhibitors of serine proteases namely serpins and a cell surface protective molecule that prevents the disruption of the cytoplasmic membrane by perforins [15].

In summation, cytotoxic CD4 positive T cells can accumulate in the skin in varied settings ranging from one of cutaneous inflammation associated with autoimmune disease to overt lymphoma. One could offer the espousal that the accumulation of this cell populace would be indicative of a lymphoma of immunosenescence exemplified by cases 2 through 4. The development of the aggressive CD30 negative cytotoxic large cell T cell lymphoma in the young man is unclear although we could not definitively rule out the role of either autoimmune disease or

a chronic viral illness in the propagation of his aggressive lymphoma. The lack of any literature to date on similar infiltrates in the skin is unclear but at least this initial small series brings attention to a new group of cutaneous lymphocytic infiltrates hallmarked by its distinctive phenotype.

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Conflicts of interest

None to declare.

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