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CD4/CD8 double-negative mycosis fungoides with large cell transformation and involvement of the lungs and leptomeninges

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Abstract

Mycosis fungoides (MF), the most common cutaneous T-cell lymphoma, classically has an indolent clinical course, with lesions slowly progressing from patch to plaque to tumor stage. In some cases, the late stages of disease involve extra-cutaneous dissemination to lymph nodes or viscera. Although this "Alibert-Bazin" type is the prototypic MF, there are several variants and subtypes of MF that may have different clinical implications for treatment and prognosis. We describe a woman whose disease course involved a variety of histopathologic and immunophenotypic variants including folliculotropic MF, granulomatous MF with loss of CD8, and then finally CD4/CD8 double-negative MF with large cell transformation and extra-cutaneous dissemination. Clinically her disease behaved as classic indolent stage IA MF for nearly two decades before transitioning to tumor stage and then, finally, involving the lungs and leptomeninges. It is important for physicians to be aware of the clinically relevant variants of MF as well as the possibility of transformation of previously stable disease both clinically and histopathologically.

Keywords: CTCL, cutaneous, dissemination, double-negative, extra-cutaneous, FMF, folliculotropic, GMF, granulomatous, large cell, LCT, MF, mycosis fungoides, T-cell lymphoma, transformation

Introduction

Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma (CTCL), is a mature T-cell lymphoma of the skin that classically without treatment progresses from patches to more infiltrated plaques and eventually to tumors, or blood involvement. It is characterized by a proliferation of small-to-medium sized epidermotropic neoplastic T cells with cerebriform nuclei [1]. These neoplastic T cells classically express CD3+, CD4+, CD8-, and CD45RO+, a mature T-helper memory phenotype [1]. This heterogenous disease often has an indolent course with a good prognosis, although aggressive subtypes involving lymph nodes, blood, or viscera can occur.

The WHO-EORT classification for primary cutaneous lymphomas lists three variants of mycosis fungoides that have distinctive clinicopathologic features: folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin [1]. Although these three variants are specifically identified as having clinical behavior that is different from classic MF, there are many other reported variants and subtypes of MF (e.g., bullous, granulomatous, hypopigmented). We discuss a patient who exhibited multiple different clinicopathologic and immunophenotypic subtypes or variants throughout her disease course including folliculotropic MF, granulomatous MF (not to be confused with granulomatous slack skin), gradual loss of CD8, and finally CD4/CD8 double-negative MF with large cell transformation.

Folliculotropic MF (FMF) is characterized by folliculotropic lymphoid infiltrates, with or without follicular mucinosis, which often clinically involves the head and neck and may be associated with alopecia [1]. This variant may be less responsive to skin-directed therapies as the deep, follicular, and perifollicular neoplastic cells are less accessible with topical treatment [1]. Folliculotropic MF may be the sole manifestation of the disease or may occur in conjunction with classic or other variants of MF. Granulomatous mycosis fungoides (GMF), a term coined in 1970 by Akerman and Flaxman, is a rare variant of MF characterized histopathologically by a granulomatous reaction in more than 25% of the dermal infiltrate [2]. Although there are no definitive studies on the implications of GMF for treatment selection or prognosis, a small retrospective case-control study found that patients with granulomatous MF progress more frequently with poorer responses to skin-directed therapies [3].

The CD4/CD8 double-negative phenotype is a rare variant of MF observed in approximately 12% of early-stage MF and much more commonly in tumor-stage MF [4]. A CD8+ variant is also associated with a high prevalence of localized hypopigmented lesions, β F1+/ δ - phenotype, and T-cell receptor (TCR) γ gene rearrangement compared to other phenotypes of MF [4]. Some CD3+CD4-CD8- MF express the γ/δ T-cell receptor [5]. Our patient's cells expressed the α/β T-cell receptor. Additionally, the double negative phenotype tends to show rapid, multifocal dissemination of tumors resistant to multiagent therapy [5]. Mycosis fungoides cells can lose their CD4 and CD8 expression during progression to the tumor stage [6]. Loss of the T-cell receptor may allow the tumor to avoid proliferation initiated through T cell activation.

Mycosis fungoides can also be classified by histologic transformation to large cells. Large cell transformation (LCT) of MF is defined as the morphologic change from small/medium-sized atypical lymphocytes to a large variant, in which >25% of the atypical lymphocytes have nuclei that are at least four times the size of normal lymphocyte nuclei [7, 8]. A 31-year retrospective analysis demonstrated the development of LCT in 1.4% of

stage I, 25% of stage IIB, and 50% of stage IV MF patients [9]. The 5-year survival rate of patients with LCT is 38%, which is much less than the 88% five-year survival rate of MF without LCT [8]. One study found that the overall survival in patients with LCT was 11.88 years for those with a solitary tumor, 5.57 years in patients with multiple localized tumors, and 3.31 years in patients with multiple generalized tumors [10]. Three clinical patterns of LCT in MF are seen, including a new, solitary nodule within a pre-existing MF patch or plaque, an abrupt onset of many persistent nodules, or a new, persistently enlarging tumor [8].

Dissemination of MF to extra-cutaneous sites, while rare, is a very poor prognostic indicator. Extra-cutaneous dissemination is observed in <10% of patients with patch or plaque disease and in 30-40% of patients with tumors or generalized erythrodermatous involvement [11]. Involvement of extra-cutaneous sites is directly correlated to the extent of cutaneous disease. The most commonly involved organs are lung, spleen, liver, and gastrointestinal tract. Patients who present with involvement of lymph nodes or viscera have a median survival of <1.5 years [11]. We describe a woman who, after many years of indolent stage IA folliculotropic MF, developed cutaneous and subcutaneous nodules, CD4/CD8 double-negative MF with large-cell transformation, and lung and leptomeningeal involvement.

Case Synopsis

We describe a 71-year-old woman who presented with a 10-year history of pruritic, erythematous, scaly patches on the right mandible, upper extremities, buttocks, and lower extremities, comprising 4% body surface area (BSA). The lesions intermittently resolved with skin-directed therapy including topical triamcinolone 0.1% cream. In 2000, two lesional skin biopsies from the right mandible and left shoulder showed the presence of multifocal epidermotropic and folliculotropic lymphoid infiltrates most consistent with the early stages of folliculotropic mycosis fungoides FMF (Stage IA). Immunohistology staining showed CD4+/CD8+, CD25-, and CD5-



Figure 1. Progression of disease with ulcerated tumor of the left buttock, scattered erythematous patches and edematous plaques of the buttocks and flanks.

phenotype. Her skin lesions initially improved with psoralen plus UVA photochemotherapy (PUVA), but PUVA was discontinued after 7 months due to cutaneous burning. Topical bexarotene 1% gel triamcinolone 1% cream resolved most lesions.

In 2001, a lesional skin biopsy of the right knee showed an atypical, CD4+/CD8- lymphoid infiltrate in the superficial dermis with epidermotropism and scattered large cells comprising less than 10% of the specimen. Routine laboratory studies were within normal limits and flow cytometry showed no peripheral blood involvement. Patch lesions on the right jaw, forehead, and knee, comprised 4.5% BSA, still consistent with stage IA MF. Her treatment regimen of topical bexarotene 1% gel and triamcinolone 1% cream controlled her skin for about one year; however, the lesions became minimally responsive to the regimen. A trial of topical nitrogen mustard was discontinued because of the development of allergic contact dermatitis. Topical bexarotene gel was re-started with clobetasol 0.05% cream and natural sunlight three days per week with a stable BSA fluctuating between 2-5% patch for the next several years.

In 2008, a skin biopsy of the left thigh showed a dermal lymphohistiocytic infiltrate with numerous eosinophils, atypical CD4+/CD8+ lymphocytes (with a ratio of 2:1), and follicular mucinosis, consistent with MF with granulomatous infiltrate. Subsequent intervention included narrow band UVB phototherapy three days per week, topical triamcinolone 0.1% cream, halobetasol 0.05% cream,

and tazarotene 0.1% cream with <5% BSA patch involvement.

Twelve years after presentation a single 3x2cm tumor erupted on the left upper extremity consistent with MF stage IIB. The lesion remained stable and did not resolve for two years on oral bexarotene 300mg daily followed by oral vorinostat 400mg daily for three months. The tumor was subsequently successfully treated with a course of local radiation therapy. However, three years after the radiation treatment, the patient developed multiple ulcerated tumors on the buttocks and flanks, encompassing 3.75% BSA. The tumors were again treated with radiation and she continued on oral bexarotene 300mg daily.

In 2017, the patient presented to the emergency department with cough and shortness of breath. Physical examination revealed an ulcerated tumor on the left buttock with black eschar, erythematous edematous plaques on the buttocks, flanks, thighs, and forearms, with a BSA of 11% patches, 4% plaque, and 2% tumors (**Figure 1**). A CT scan revealed a 5.0cm left lower lobe lung mass (**Figure 2**). Needle core biopsy of the mass showed an atypical lymphoid infiltrate of CD3+ positive and CD4, CD5, CD7, CD8, CD15, CD20, CD30 negative, small-to-large cells consistent with T-cell lymphoma. Bone marrow biopsy and flow cytometry showed no involvement of lymphoma. Her disease was restaged as MF IVB. The left lower lobe lung mass was treated with 20Gy of radiation therapy and the cutaneous tumors of the gluteal and flank regions were treated with 16Gy

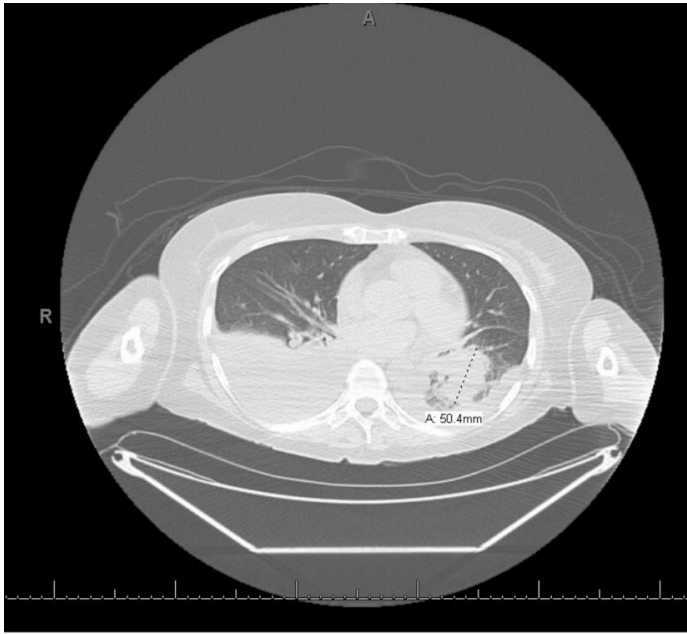


Figure 2. Abdominal CT scan demonstrating the 5.0cm left lower lobe lung mass.

with improvement (**Figure 3**). One month later, she restarted oral bexarotene at 300mg/day, topical bexarotene 1% gel, and clobetasol 0.05% cream. A PET-CT scan showed a decrease in size of the patient's lung mass and numerous new cutaneous nodules of the back and groin. Her BSA was noted to be 3.9% patches, 0% plaques, and 3.75% tumors. Pralatrexate 15mg/m² once weekly × three weeks out of four was added two months after radiation but was discontinued with bexarotene a month later because of the development of several tumors on her bilateral arms, legs, and trunk that degraded to



Figure 3. Improvement of the left buttock tumor after radiation therapy.

necrotic ulcers. The recent lung mass, skin ulceration, and disease progression on pralatrexate was clinically concerning for large-cell transformation (LCT). A cutaneous biopsy of the right arm lesion showed a CD3+, CD4-/CD8-, and CD7- atypical lymphoid infiltrate of greater than 25% large cells with extensive epidermotropism, consistent with double-negative MF with large-cell transformation (**Figure 4**). Most lymphocytes expressed TCRβ1 and anti-TCRγ labeled rare cells. Monoclonal TCR β and γ chain gene rearrangements were detected by PCR. Her oncologist prescribed 50mg oral etoposide per day for two weeks followed by one week of filgrastim and then repeated, which improved her skin lesions and lung mass. Her improvement was evidenced by a decrease in her tumor burden from 3.45-3.75% in July 2017 to 1.0% in January 2018 and a decrease in her modified skin assessment tool from 6.5% to 4.5% in the same time frame.

However, after 8 months on that regimen, she presented to the emergency department with a one-month history of headache, tinnitus, vertigo, ataxia, dysphagia, and right facial droop. MRI of the brain and spine revealed C1-C5 cord edema with an epidural tumor at C2. Diagnostic lumbar puncture showed no signs of infection and CSF pathology showed atypical lymphoid cells in a background of abundant eosinophils and neutrophils, consistent with leptomeningeal disease from her T-cell lymphoma. The radiation oncology department treated the cerebrospinal axis with palliative radiation therapy for two weeks before she was placed in home hospice.

Case Discussion

Our patient's non-specific dermatitis 10 years prior to presentation was likely undiagnosed stage IA MF. Once she was diagnosed with MF her disease remained stable at stage IA for 12 more years. Her MF presented as both folliculotropic MF (biopsy of the head and neck) and granulomatous MF (biopsy from the thigh) during this early stage and was controlled with a variety of skin-directed therapies and phototherapy. Mycosis fungoides later progressed to stage IIB MF when a single tumor arose and was successfully treated with a course of local radiation.

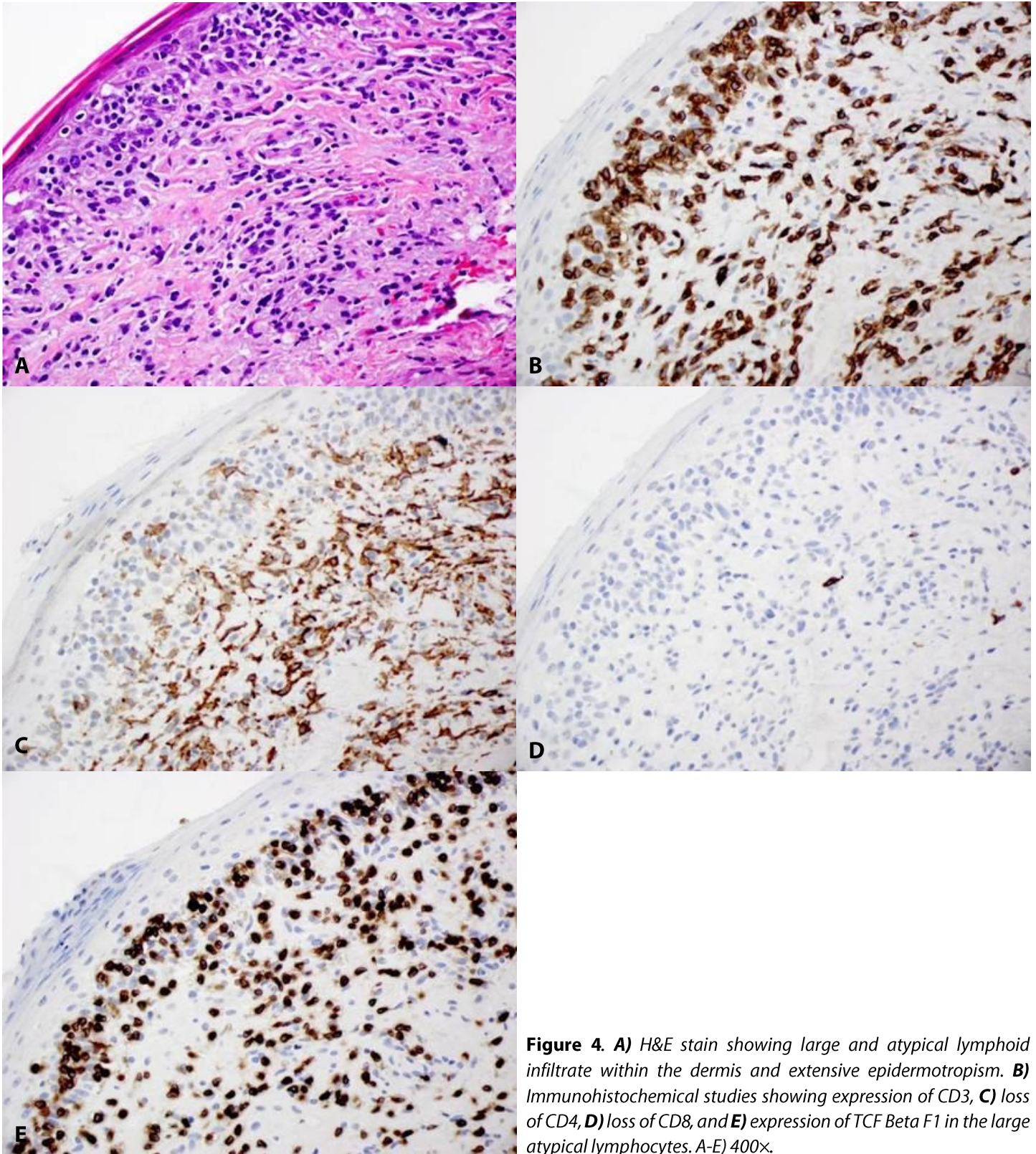


Figure 4. **A)** H&E stain showing large and atypical lymphoid infiltrate within the dermis and extensive epidermotropism. **B)** Immunohistochemical studies showing expression of CD3, **C)** loss of CD4, **D)** loss of CD8, and **E)** expression of TCF Beta F1 in the large atypical lymphocytes. A-E) 400x.

Almost two decades after initial presentation, she developed more skin tumors as well as extracutaneous dissemination of her disease consistent with stage IVB MF with CD4-/CD8- cells and large cell

transformation of her disease. The atypical cells found in both our patient's lung biopsy and the most recent skin biopsy were CD3+/CD4-/CD8-, often referred to as doubled-negative CTCL. Our patient's

disease demonstrated behavior associated with the double-negative immunophenotype, including rapid, multifocal dissemination and resistance to multiagent therapy. It is well known that MF cells can lose both CD4 and CD8 expression during progression to the tumor stage, which would explain why our patient's disease began as CD4+/CD8- cells but became double-negative late in the disease. Additionally, the patient's rapid, generalized eruption of multiple tumors of the anterior trunk, posterior trunk, and bilateral arms and legs within a few months was consistent with the clinical presentation of LCT.

Her advanced clinical stage of IVB at the time of LCT diagnosis, extra-cutaneous lung involvement, age greater than 60, and CD30- cells conferred a worse prognosis than patients without those factors. The initial stability of her disease for decades with normal range LDH and $\beta 2$ microglobulin levels were interesting findings not typically seen in patients who later develop widespread tumors and visceral involvement.

Reports of lung involvement in MF are few. One case of lung involvement was documented in 1915 and another in 1948 [12]. In 1974, a study on the systemic involvement of MF found lung involvement in 21 of 32 autopsy patients [13]. However, the reliability of such findings at this time is questionable due to evolving terminologies and criteria for diagnosis. An analysis of 710 patients with CTCL studied retrospectively at our institution showed that patients with pneumonia or lung involvement, including nodules, portend poor survival [14]. Lung involvement was rare, with less than 1% of patients affected, and median survival was 28 months for those with pneumonia and 41 months for those with other lung involvement [14]. Because the atypical lymphoid cells found in our patient's lung nodule biopsy showed the same morphology and immunophenotype as her most recent cutaneous biopsy, the lung involvement was most likely related to the patient's extra-cutaneous dissemination of MF with LCT.

Central nervous system (CNS), brain, and meningeocerebral involvement is also rare and has devastating consequences. The incidence of CNS

involvement in several large clinical cohorts is less than 1.6% [17]. A review of 9 reported cases with CNS involvement all had concurrent lymph node and visceral involvement [12]. A case series of 5 patients found that patients with LCT have a greater risk of CNS involvement compared to their non-transformed counterparts [15]. Our patient's extra-cutaneous dissemination involving the CNS was likely related to LCT and the lack of treatment options in this advanced disease stage left her with only palliative therapy options.

Conclusion

Mycosis fungoides is a heterogeneous skin T-cell lymphoma with a broad range of clinical and histopathological presentations. Clinically, our patient's disease began as stage IA patch and plaque MF for decades, transitioned to stage IIB tumor MF responsive to radiation, and finally progressed to stage IVB MF with widespread cutaneous tumors and metastases. Our patient's disease was unique in that she manifested several histologic variants during the course of her illness. Her skin biopsies first demonstrated folliculotropic MF, then granulomatous MF with gradual loss of CD8, and finally CD4/CD8 double-negative MF with LCT in both the cutaneous tumors and lung biopsy. This patient's presentation highlights a novel entity of CD3+/CD4-/CD8- double negative MF with α/β TCRs, LCT, and extra-cutaneous dissemination of transformed large cells to the lung and leptomeninges. This case shows that progression of clonal T cells can produce rare immunophenotypes, especially loss of the T-cell receptor. It is important for physicians to be aware of the possibility of transformation of previously stable disease both clinically and histopathologically. Physicians should also be aware of the factors that are associated with a poor prognosis including clinically advanced stage at large-cell transformation, extra-cutaneous involvement, age greater than 60, CD4-CD8- double negative phenotype, and CD30- cells as seen in this patient. Patients with progression of their disease, especially with tumors or new histologic subtype, should be evaluated with repeat biopsy, systemic imaging, and repeat flow cytometry.

Potential conflicts of interest

The authors declare no conflicts of interest.

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