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ORIGINAL ARTICLE

Two cases of phenotypic switch of primary cutaneous T cell lymphoma after treatment with an aggressive course and review of the literature

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Abstract

A "phenotypic switch" (PS) is a well-known phenomenon that occurs in hematopoietic neoplasms, often after treatment. However, in cutaneous T cell lymphoma (CTCL), this event has rarely been reported, and thus, very little is known about its relevance to disease prognosis. We report two cases of patients that were diagnosed with a CD4+ mycosis fungoides with positive T cell receptor gene rearrangement studies. Both patients originally responded to treatment, but subsequently, their CTCL came back with a different phenotype of a CD4− CTCL. Gene rearrangement studies were performed on the second occurrence in order to prove that this was the same lymphoma. Both patients died from their CTCL. Additionally, we collected seven cases of primary CTCL from the literature with tissue samples from before and after treatment with molecular studies confirming these neoplasms contained the same T cell clone, providing evidence of a true PS. This too revealed a poor prognosis in the majority of these cases. CTCL should be worked up to determine whether a PS has occurred after therapy since it could confuse management of patients and appears to portend a poor prognosis.

Keywords Phenotypic switch · Cutaneous T cell lymphoma · Mycosis fungoides · Poor prognosis

Introduction

Differentiating a recurrent lymphoma from a second primary lymphoma is often difficult. In the past, a lymphoma in a patient with a history of a similar lymphoma was considered a recurrence [1]. However, presently, the ability to discern a recurrence from a new lymphoma is simple using gene rearrangement studies [2]. One reason this is necessary is the ability of hematopoietic tumors to have a "phenotypic switch" (PS) [3–5]. A PS usually occurs after treatment and is defined by a tumor retaining its genetic signature, but its phenotype is altered.

A PS is a phenomenon that has rarely been reported with regards to cutaneous T cell lymphoma (CTCL), which most commonly manifests itself in the form of mycosis fungoides (MF) [6]. However, recognizing a PS in a MF patient, instead of a second primary lymphoma, is necessary. The reason for this is that in MF, the recognition of the same T cell clone in two different locations has been shown to be prognostically significant [7]. Therefore, if a PS occurs and it is not recognized, a patient may have an altered treatment and a worse clinical course than expected.

PS is a rarely reported phenomenon in the literature by many hematopoietic neoplasms. There have been authors who suggest that a PS by CTCL is related to a worse prognosis, but that is based on few cases or single case reports [8–13]. Herein, we add an additional two cases to the literature and review the currently available cases of CTCLs with a PS to shed light on this phenomenon and to possibly understand the meaning of whether a true PS with the same T cell clone has any clinical impact.

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Case presentations

The first case is a 92-year-old female with a history of stage III colorectal cancer who presented to her dermatologist with pruritic and flakey skin lesions on her ears, face, and chest. A biopsy of the left cheek and scalp performed a few months later revealed a lichenoid deep, periadenexal, and severely epidermotropic infiltrate of large mononuclear cells in the dermis and epidermis which demonstrated CD3 and CD4 (4:1 CD4/CD8) (Fig. 1), but had a 40–50% decreased expression of CD7. βF1, TCRδ, Granzyme B, and TIA-1 were negative as well. T cell receptor gene rearrangement studies were performed and showed monoclonal peaks in the gamma (V1–8, 255 bp and V11, 155 bp) and beta regions (Tube C 312 bp) (Fig. 2). This led to the diagnosis of mycosis fungoides stage IIB. A PET/CT scan confirmed that the CTCL was confined to the skin and subcutis. She was subsequently started on cyclophosphamide, prednisone, and etoposide which her lesions initially responded to and shrunk.

After 6 months of therapy, her lesions returned and began to enlarge. A second biopsy was performed of an ulcerated cutaneous chest wall lesion which revealed diffuse sheets of medium- to large-sized neoplastic lymphocytes. Some of the neoplastic cells were rimming adipocytes and had a panniculitis-like pattern, but extensively involved the dermis as well. There was no identifiable epidermis located on any sections. Flow cytometry revealed that the cells expressed CD3, CD26, CD45, CLA (cutaneous lymphocyte-associated antigen), TCR γδ, Granzyme B, and TIA-1, but not CD2, CD4, CD5, CD7, CD8, CD30, CD56, or TCRαβ (Fig. 3). Immunohistochemistry was done and showed positivity for TIA-1, Granzyme B, and CD3, but was negative for CD5 and CD7 (Fig. 4). Additionally, a TCR gene rearrangement study was performed that showed that the same gene rearrangements present as mentioned above, providing proof that this was the same neoplasm as previous (Fig. 5). These findings led to the diagnosis of a cutaneous γδ T cell lymphoma. Within a month of this final diagnosis with such a poor prognosis, she succumbed to the disease and passed away.

The second case was a 58-year-old female who presented to her dermatologist with erythematous and scaly plaques. A biopsy was performed and revealed a dense band like infiltrate of lymphocytes with prominent epidermotropism. Immunohistochemical stains were performed and revealed that the infiltrate was CD3+ and had many more CD4+ cells than CD8+ cells (5:1) with significant loss of CD7 and Granzyme B was negative (Fig. 6). Additionally, T cell recep-

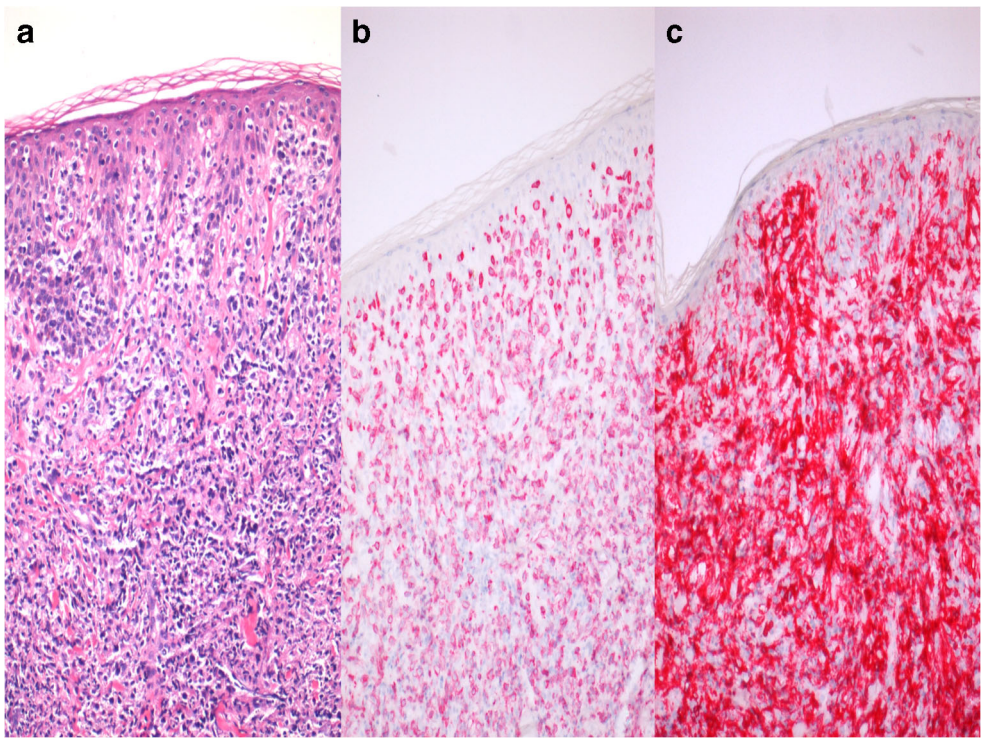

Fig. 1 Initial biopsy of case #1. **a** There is a lichenoid deep, periadnexal and severely epidermotropic infiltrate of small to medium-sized atypical lymphocytes with occasional large mononuclear cells (H&E, 20×). **b** The neoplastic cells are positive for CD3 (20x). **c** The neoplastic cells are positive for CD4 (20×)

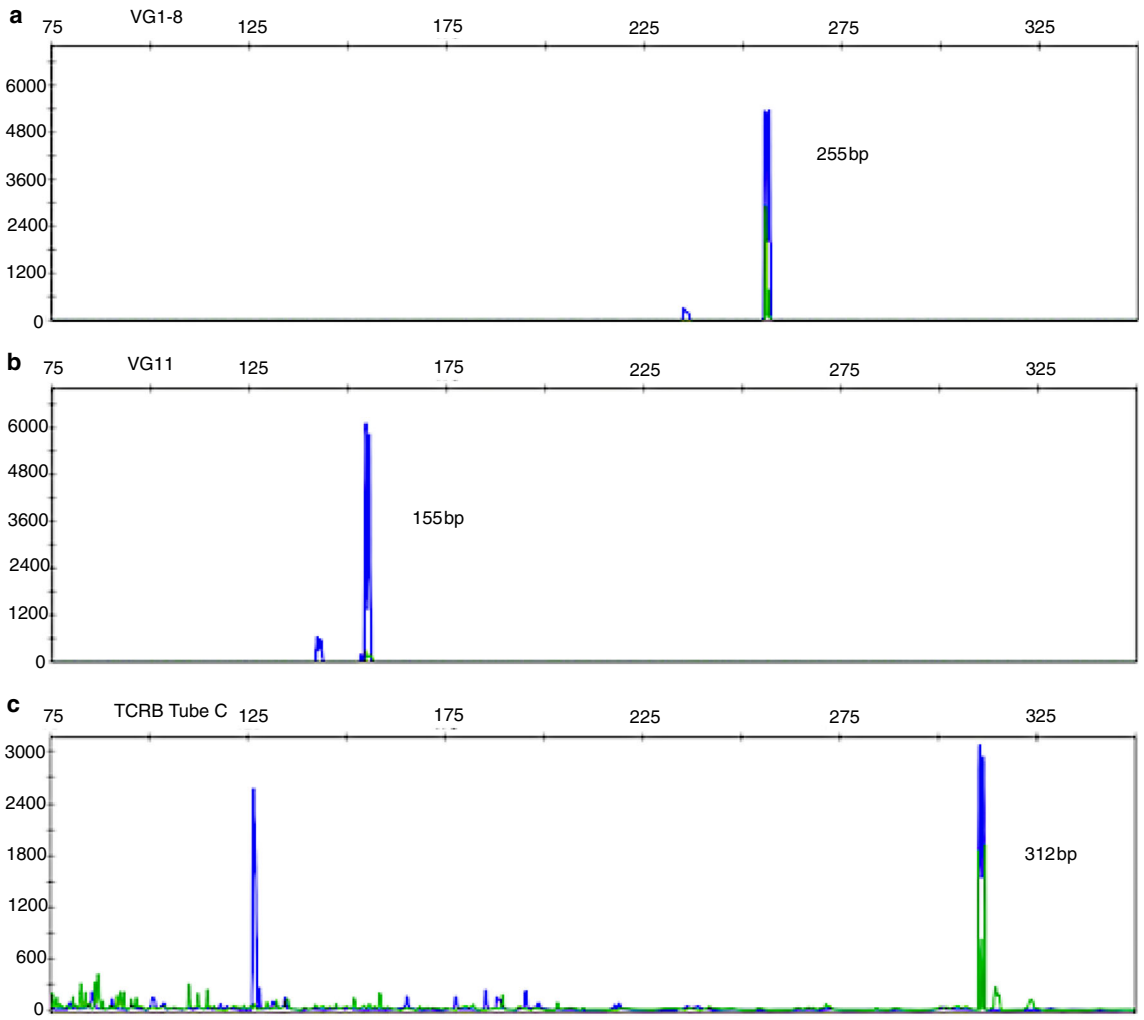

Fig. 2 Initial T cell receptor gene rearrangement studies of case #1 showing **a** one peak in the V1–8 gamma region, **b** one peak in the V11 gamma region, and **c** one peak in the beta region in tube C

tor gene rearrangements revealed a monoclonal peak in both the gamma (VG1–8, 254 bp) and beta regions (Tubes A, 256 bp, and C, 297 bp) (Fig. 7). The patient was diagnosed with mycosis fungoides stage IIB. She was treated with topical steroids, phototherapy, and radiation therapy.

Thirteen years later, she returned with worsening lesions and now had gastrointestinal complaints. Therefore, another biopsy was performed of her cutaneous lesions and her stomach. Both revealed large atypical cells, but now, they were positive for CD2, CD3, CD7, Granzyme B, with a Ki67 of 80% and they were negative for CD4, CD5, CD8, CD20, CD25, CD30, CD56, ALK1, TIA1 (Fig. 8). T cell receptor gene rearrangements were performed on the stomach biopsy which revealed the same rearrangements present as previously (Fig. 9). Plans were made to start her on systemic chemotherapy, but she passed away shortly after her recurrence diagnosis.

Methods

Review of the literature

In addition to our case reports, a PUBMED search was performed looking for published cases of CTCL that had undergone a PS and had gene rearrangement studies to prove the presence of the same T cell clone. We recorded the immunohistochemistry studies, stage of disease if

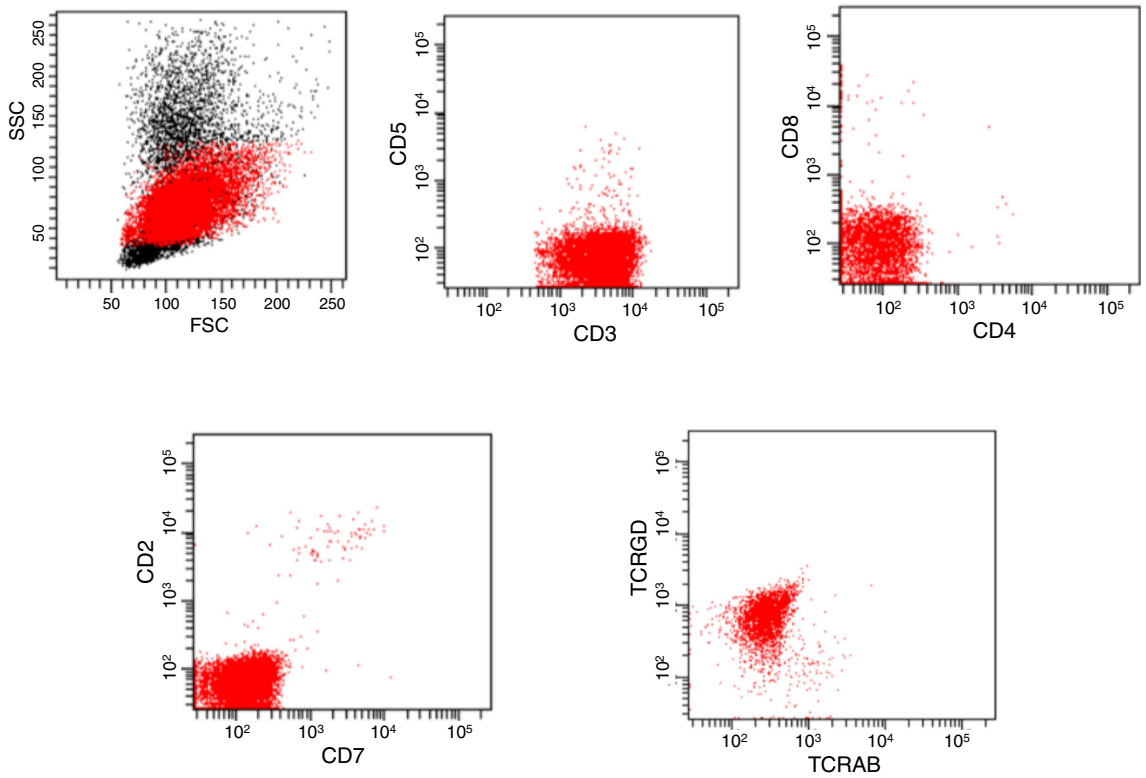

Fig. 3 Flow cytometry histograms showing the neoplastic T cells (red) are positive for CD3 and TCR GD, but negative for TCR AB, CD2, CD4, CD5, CD7, and CD8

available, and clinical outcomes. Patients were excluded if they did not have a diagnosis of a primary cutaneous T cell lymphoma or if they did not have a TCR gene rearrangement study proving the presence of the same clone.

Immunohistochemistry

Immunohistochemical staining was performed during the original diagnostic work-up of the cases by the use of

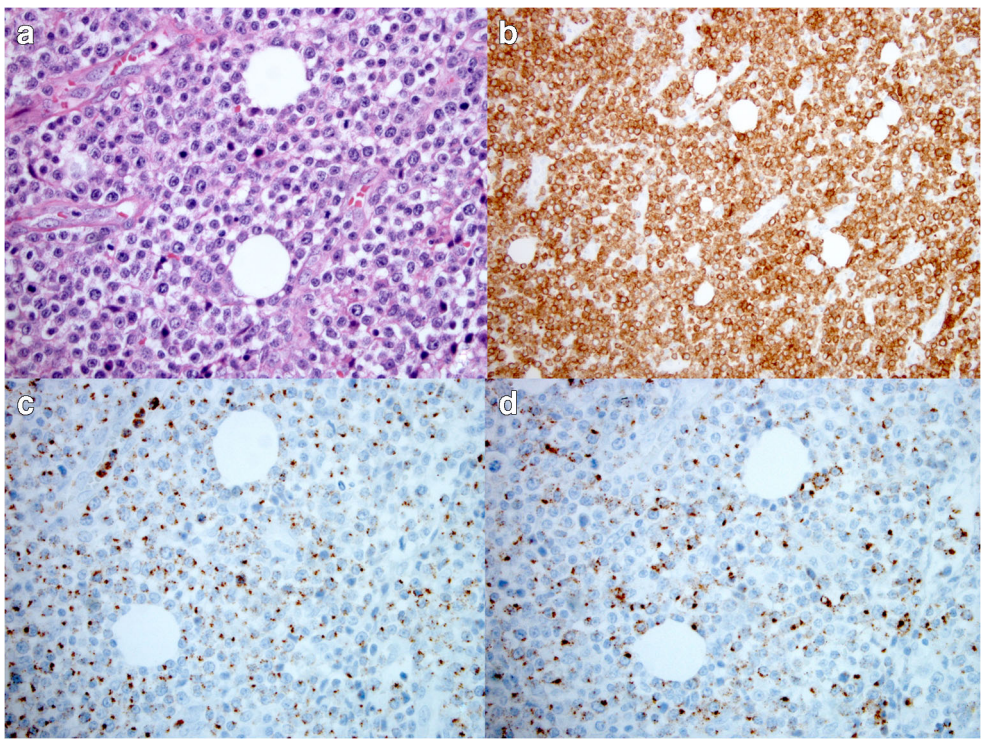

Fig. 4 Subsequent biopsy of the ulcerated lesion in case #1. It shows **a** diffuse sheets of medium- to large-sized neoplastic lymphocytes, some cells rimming adipocytes, in a panniculitis-like pattern. The cells have coarsely clumped chromatin with some large cells with vesicular nuclei and prominent nucleoli (H&E 40×). **b** The neoplastic cells are CD3 positive (20×). **c**, **d** TIA-1 and Granzyme-B, respectively, showing cytotoxic phenotype (40×)

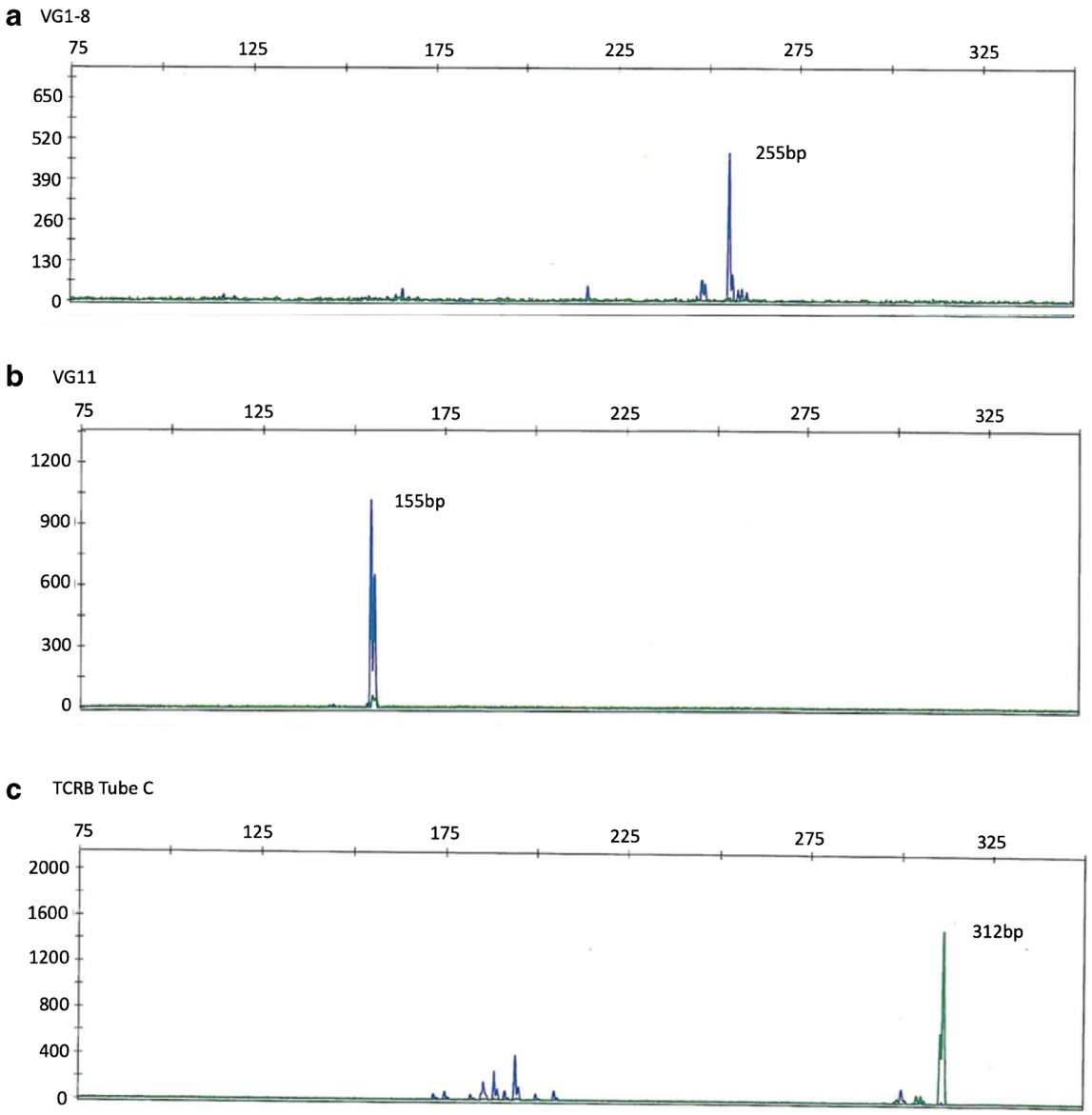

Fig. 5 Subsequent T cell receptor gene rearrangement studies of case #1 showing the same gene rearrangements **a** one peak in the V1–8 gamma region, **b** one peak in the V11 gamma region, and **c** one peak in the area of gaussian distribution in the beta region in tube C

formalin-fixed paraffin-embedded tissue sections and an automated immunostainer (Dako, Carpinteria, CA, USA). Antigen retrieval was performed with either a citrate buffer (pH 6.1), EDTA buffer (pH 9), or Trilogy. Our laboratory uses the Dako EnVision+ system, horse-radish peroxidase two-step immunohistochemical staining technique. The specific immunohistochemical stains used were CD3 (1:100, F7.2.38), CD8 (1:200, C8/144B), CD56 (1:100, 123C3), Granzyme B (1:25, GrB-7), Ki67 (1:50, MIB-1) (Dako North America), and CD4 (1:25, 4B12) (Thermo Scientific) and TIA-1 (1:200, 2G9A10F5) (Beckman Coulter). Similar methods were used for the other immunohistochemical stains. A case was scored as positive for each marker if there was staining in > 20% of the neoplastic cells with the appropriate localization for the specific stain and with appropriate staining of controls.

TCR gene rearrangement method

TCR studies were performed at the time of diagnosis on formalin-fixed paraffin-embedded (FFPE) tissue. Deparaffinization and DNA extraction were performed. Briefly, 20–30 sections of the FFPE tissue were cut at a thickness of 5 μm. The tissue sections were incubated in a detergent made of d-Limonene and Butylated

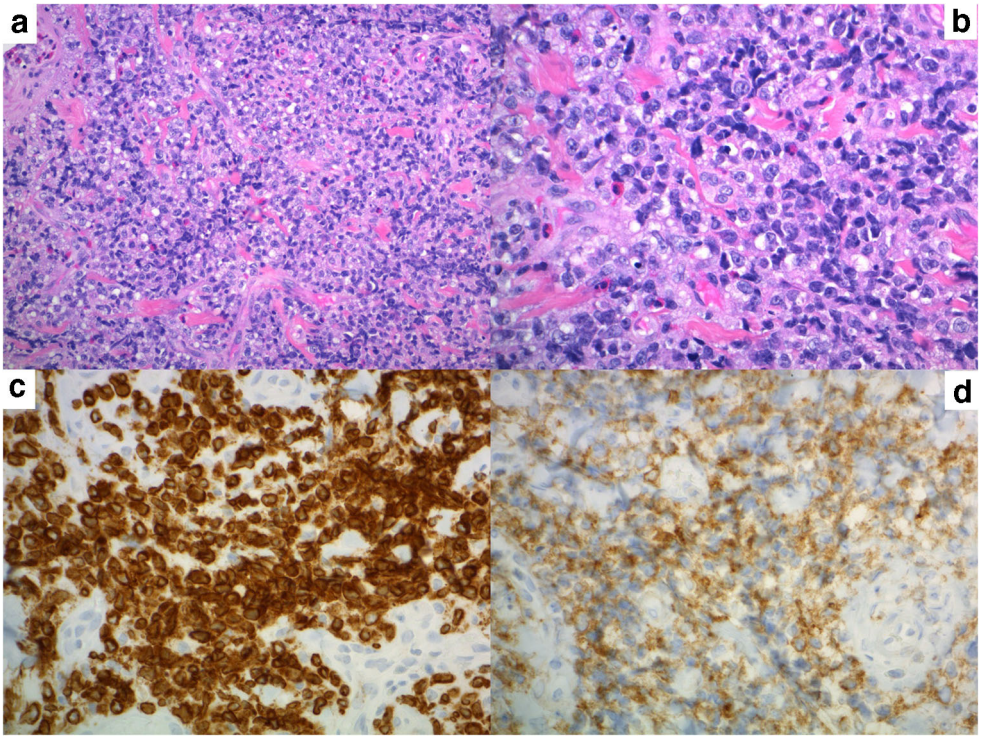

Fig. 6 Initial biopsy of case #2. **a**, **b** Dense infiltrate comprised large atypical cells that are **c** positive for CD3 and **d** CD4

hydroxyanisole. The tissue mixed with detergent was then centrifugated and the detergent was removed and EtOH was added, and the specimen was incubated for another 5 min, centrifugated for 5 min, and then the tissue was washed with EtOH. PK buffer was added proportionally to the size of the pellet, approximately 2–3 times the size, and a pinch of PK powder was added. The sample was digested for at least 2 h in a 37 °C incubator. Another pinch of PK was added to the sample and incubated at 60 °C for 1–3 nights with shaking at 150 RPM. The DNA was then purified using a Qiagen DNA mini kit (QIAGEN Str. 140724 Hilden, Germany). Polymerase chain reaction was performed on genomic DNA. The TCR gamma V1-8-J, V9-J, V10-J, and V11-J regions and/or TCR beta gene V-J and D-J regions were amplified. The amplified products were analyzed using capillary electrophoresis with the ABI Genetic Analyzer (Waltham, Massachusetts, USA). T cell receptors were analyzed using a set of multiplex primer sets (BIOMED-2), which were purchased from Invivoscribe Technologies (San Diego, CA). As is the interpretive guidelines in our laboratory, only one or two peaks that are three times the size of the background were considered monoclonal. Any case containing three or more peaks was considered oligoclonal or polyclonal and excluded from further analysis.

Results

In addition to our cases, we collected a total of seven patients from our review of the literature with any diagnosis of a CTCL that had undergone a PS. All patients had TCR gene rearrangement studies performed on samples before and after treatment providing evidence that the T cell clone was the same.

The age range for this group was 46–91 years old (mean of 67 years old) and the M/F ratio was 6:3. As stated above, each patient had TCR gene rearrangement studies proving the tumor was made up of the same clone before and after treatment. Also, everyone in this group had a PS either from a CD4+ T cell lymphoma to a CD8+ phenotype or to a cytotoxic phenotype that was CD4−/CD8−. The clinical stages of the patients included IA, IB, IIB, and IVA. One patient did not have an initial recorded stage. Seven of the patients had DOD, one patient was in remission, and one patient had stable disease. All patients had a PS from a CD4+ phenotype (Fig. 3) to a cytotoxic (Fig. 4) or a CD8+ phenotype. Treatments between the two biopsies that revealed a PS in this group included phototherapy, excracorporeal photopheresis, bexarotene, cyclophosphamide, adriamycin, vincristine, prednisone, radiation therapy, and stem cell transplant, among others. Findings are summarized in Table 1.

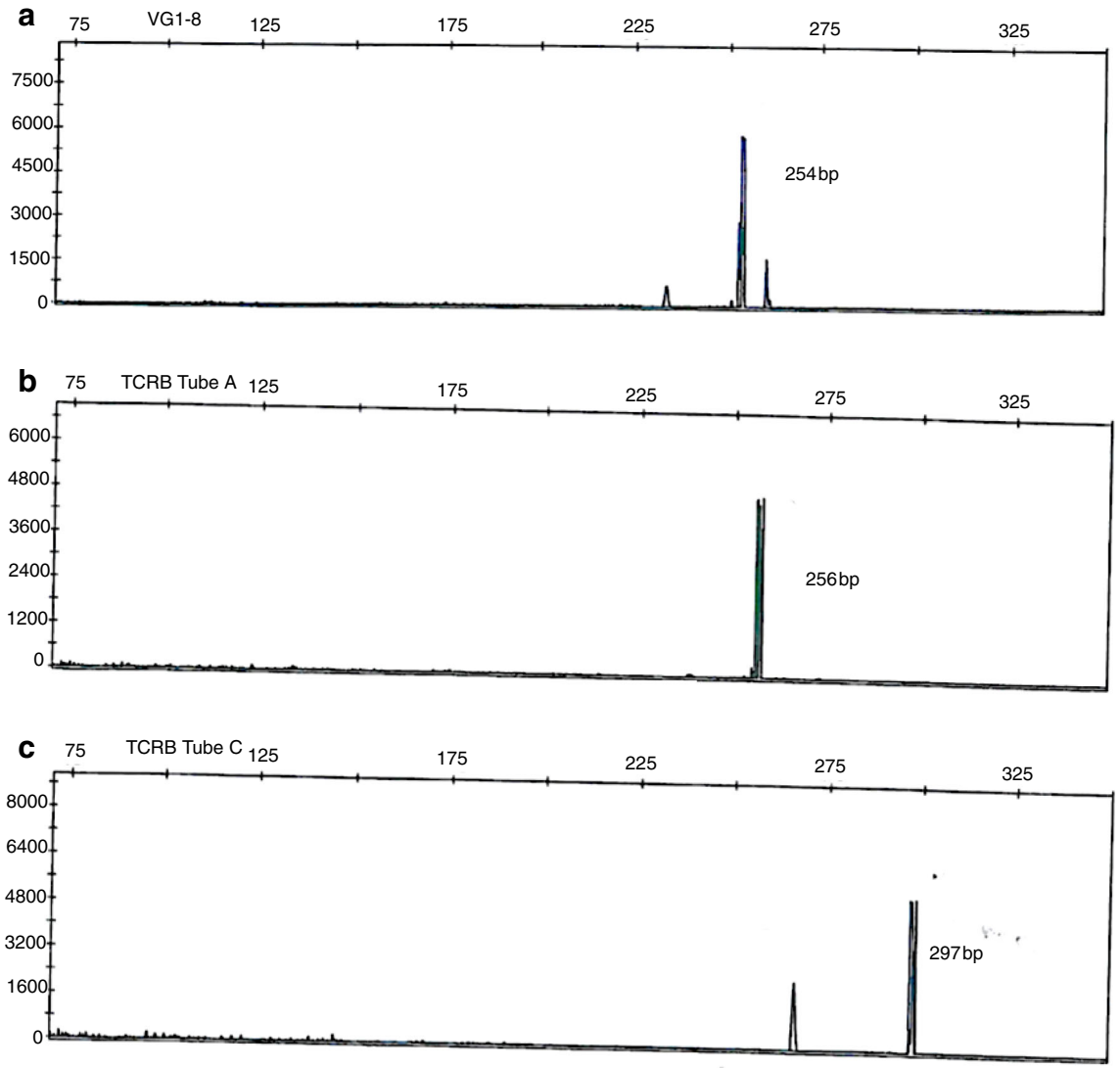

Fig. 7 Initial T cell receptor gene rearrangement studies of case #2 showing **a** one peak in the V1–8 gamma region, **b** one peak in the beta region tube A, and **c** one peak in the beta region in tube C

Discussion

CTCL is often a difficult to identify disease that requires a keen eye to detect. Therefore, histologic criteria have been developed to aid the pathologist in diagnosis [14]. However, one of the most sensitive tools in the pathologist's armament for diagnosing all types of CTCL is the TCR gene rearrangement molecular test which has been shown to detect up to 94% of clonal T cell populations [15]. Another method used to aid in the diagnosis of CTCL is immunohistochemical staining patterns, as the usual phenotype is CD3+, CD4+, CD8−, and there is a decreased expression of CD7 [16, 17]. This method can be used in many instances in place of TCR gene rearrangement studies, especially when these molecular studies are unavailable. In fact, many pathologists use immunophenotype to follow MF/CTCL to ascertain if a tumor is a continuation of a clonal process or a second primary lymphoma. This can lead to a diagnostic dilemma as Nikolova et al. initially showed that a PS can occur from a CD4+/CD8− to a CD4−/CD8+ phenotype, even in tumors that are identified to be the same T cell clone by TCR gene rearrangement studies [18].

Recognizing the difference between a PS and a second primary CTCL is of the utmost importance as Washington et al. have reported that CTCLs have "stable phenotypically

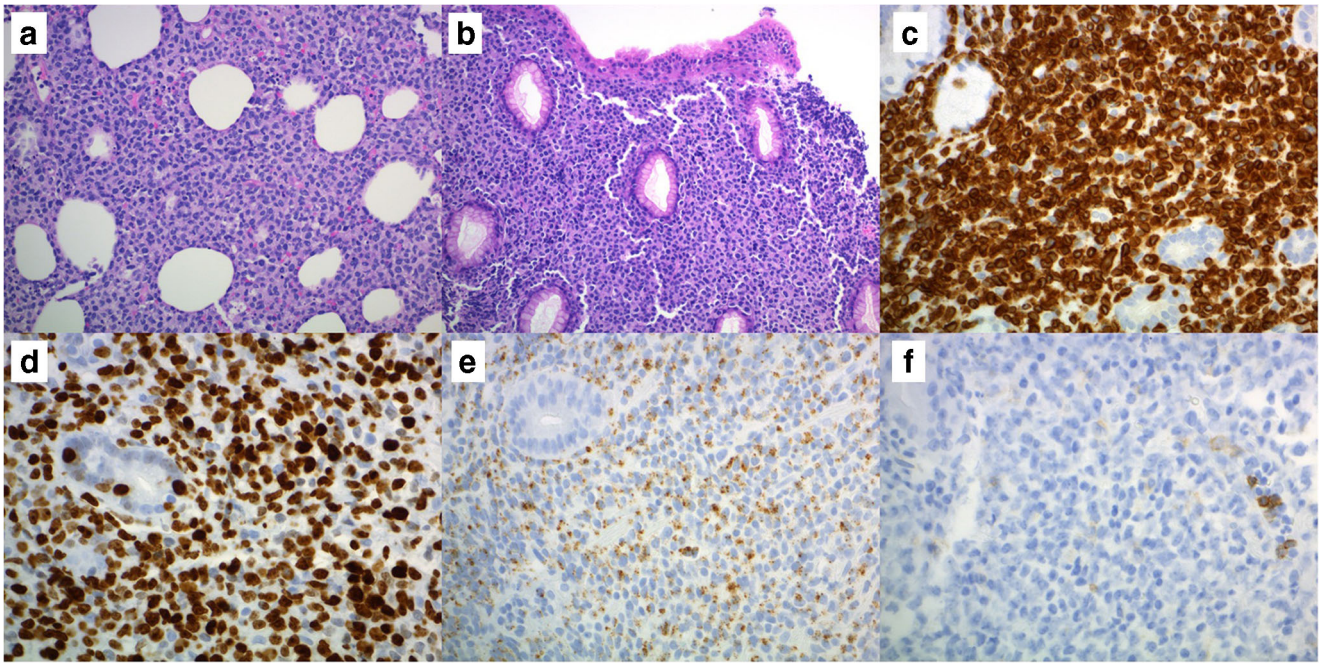

Fig. 8 Subsequent biopsy of the skin in case #2 shows **a** diffuse sheets of medium- to large-sized neoplastic lymphocytes some having vesicular nuclei and some having hyperchromatic nuclei (H&E 20×). **b** Similar findings in the stomach biopsy. **c** The neoplastic cells are CD3 positive (40×). **d** The cells show a high percentage of positivity for Ki-67 (40×). **e** The cells are now positive for Granzyme-B, showing cytotoxic phenotype (40×). **f** However, the cells are now negative for CD4 (40×)

aberrant T-cell populations … and can be used to monitor response to therapy." [19] Therefore, if a phenotypic switch does occur and this method is used, clinical management will be altered and the patient's outcome could be uncertain.

We identified seven cases in the literature [8–13] of patients with a PS with the same T cell clone present and two cases from our own institution. A PS in CTCL is thought to be a rare occurrence, but another possibility is that it is simply a poorly recognized phenomenon that is missed. Nevertheless, in these nine cases, the PS occurred after treatment for the patient's CTCL was begun and it appears to portend a worse prognosis, as 7/9 of these patients DOD.

This phenomenon of phenotypic switch has previously been described in primary cutaneous γδ T cell lymphoma in a series of nine cases [20]. This case series considered the lymphoma to have an immunophenotypic switch if any antigen was different between the first and subsequent biopsies. They found that there was at least one case of the nine that had a shift of either increased or decreased expression of CD4, CD5, CD7, CD8, CD30, CD56, TIA-1, granzyme B, TCRγ, and TCRβ. However, only four of the cases were confirmed to have the same molecular signature by PCR methods. Therefore, it seems uncertain whether the other five cases represent a true phenotypic switch or a new lymphoma that subsequently developed. Our cases are both unlikely to have been primary cutaneous γδ T cell lymphomas since the first biopsy of the first case was negative for TCRδ. Additionally, the time between the first and second biopsy of the second case was 13 years, which is highly unlikely with primary cutaneous γδ T cell lymphomas [21], and the original phenotype is inconsistent with a γδ phenotype since CD4+ primary cutaneous γδ T cell lymphomas are exceedingly rare.

The positivity for γδ of the subsequent biopsy of the first case does raise the question, how does one differentiate between a primary cutaneous γδ T cell lymphoma and a case of MF with a γδ phenotype? Two different histologic patterns have been recognized by primary cutaneous γδ T cell lymphoma, strictly epidermotropic and dermal [22]. The histologic pattern that involves the dermis with or without the subcutis has been shown to have a much worse prognosis than the pattern that strictly involves the epidermis with minimal involvement of the dermis (epidermotropic). Differentiating MF from primary cutaneous γδ T cell lymphoma appears to only be necessary in the dermally involved γδ T cell lymphoma variant, since that has a worse prognosis even when matched for stage. The epidermotropic version appears to have a similar prognosis to MF of a similar stage, but has been shown to appear at a more advanced stage than typical MF [22]. Although it is rare to have a γδ phenotype by MF, it has been reported and the only true way to differentiate these entities are with clinical correlation and follow-up [23].

Why do some cases of CTCL have a PS while others keep the same immunophenotype? If there were no TCR gene rearrangements performed, this could simply be answered with the idea of clonal heterogeneity revealed by Vega et al. [24] They showed that there are several cases of MF where a

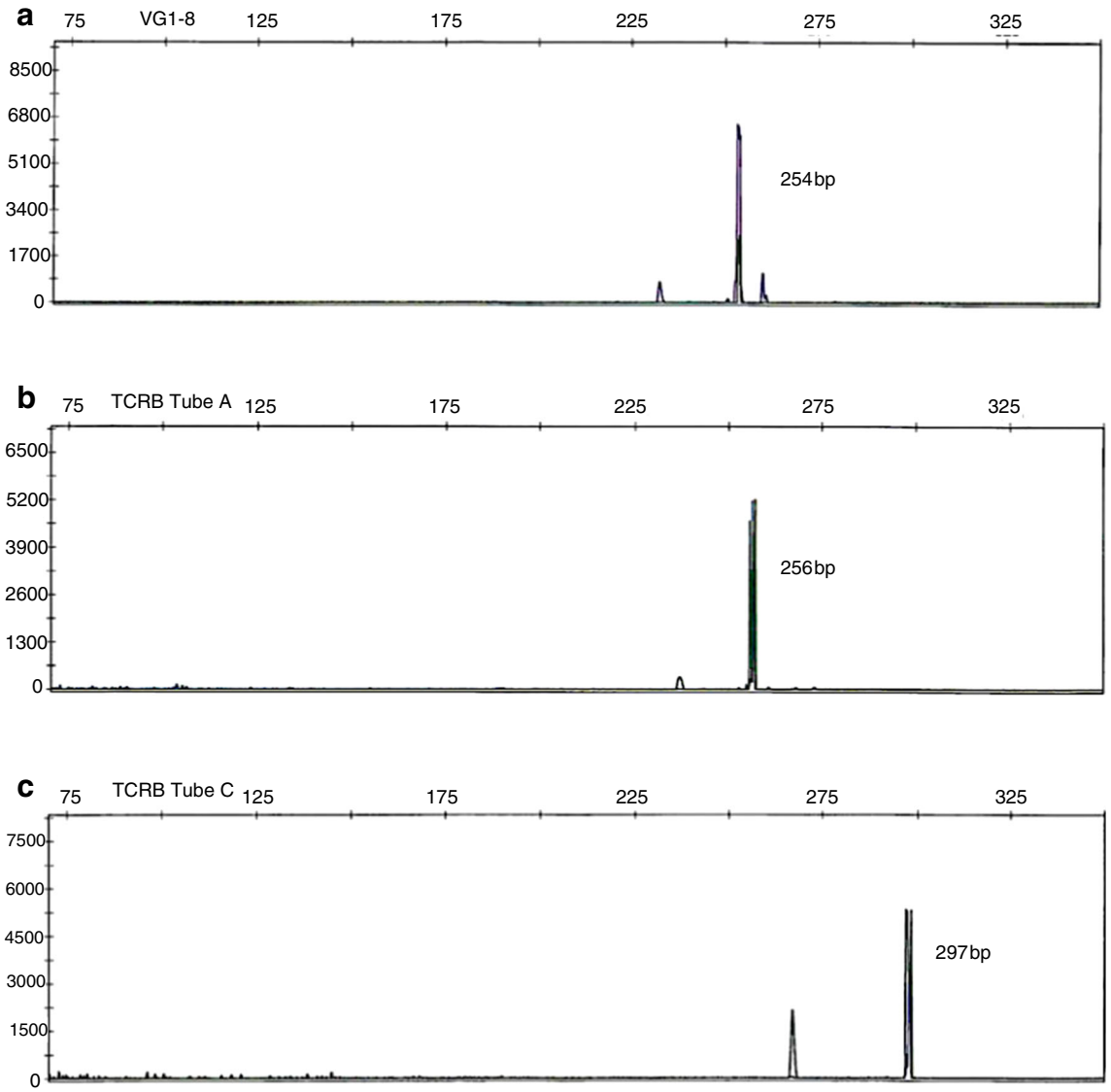

Fig. 9 Subsequent T cell receptor gene rearrangement studies of case #2 showing **a** one peak in the V1–8 gamma region, **b** one peak in the beta region tube A, and **c** one peak in the beta region in tube C

subsequent biopsy of MF in a different location can have a different TCR gene rearrangement, revealing a different T cell clone. However, in our cases, the TCR gene rearrangement studies have proven that we are dealing with the same T cell clone. Therefore, how can we explain the PS?

One possible explanation for a phenotypic switch by CTCL is based on the idea that thymic T cells that are CD3+/CD4+/CD8+ become mature high density CD3+ single CD4+ or CD8+ T cells able to respond to foreign antigen. Boumsell et al. found that a single clone of CD3+/CD4+/CD8+ T cells could be multipotent, able to give rise to both single CD4+ or CD8+ T cells [25]. Theoretically, this could explain our PS with the same T cell clone as proven by TCR gene rearrangement studies. A case of CTCL that undergoes PS could be a case of a neoplastic CD3+/CD4+/CD8+ thymic T cell. The thymic T cell clone could be predominantly producing a central CD4+ T cell that travels to the skin and, after therapy, it could start producing predominantly a CD8+ T cell. Additionally, for cases that subsequently reveal a cytotoxic phenotype with CD4−/CD8−, this process would involve an even more immature thymic T cell, capable of greater multipotency. This would also explain the seemingly aggressive behavior seen in our cases of a PS because the more immature a cell is the more aggressive it has been shown to be [26, 27].

Conclusion

Our cases, along with the review of the literature, show that a PS appears to portend a bad clinical outcome. However, the

Table 1 Features of primary cutaneous T cell lymphoma patients with a phenotypic switch after therapy

	From	Age	Sex	Race/ ethnicity	Stage	Initial phenotype	Second phenotype	TCRGR in first and second samples	Treatment between phenotypic switch	Clinical outcome
Patient 1	Marks et al.	92	F	Black	IIB	CD3+, CD4+, CD8−, βF1−, TCRδ−, Granzyme B−, TIA-1−	CD3+, CD4−,CD8−, CD30− Granzyme B+, TIA+, γδ+, αβ−	Match	Phototherapy, Cytoxan, Etoposide, prednisone, RT	DOD
Patient 2	Marks et al.	58	F	Hispanic	IIB	CD3+, CD4+, CD7−/+, CD8−, Granzyme B−	CD3+, CD4−, CD7+, CD8−, CD30− Granzyme B+	Match	Phototherapy, RT	DOD
Patient 3	Aung et al.	67	M	White	At least IIIB	CD4+, CD8−	CD8+, TIA+, Granzyme B+	Match	NR	DOD
Patient 4	Aung et al.	54	F	Hispanic	At least IIIB	CD4+, CD8−, CD5−, CD2−	CD8+ CD7+, βF1+, Granzyme B+, CD2 partially lost, CD5(−), CD45RO(−), CD30(−), EBER(−).	Match	Bexarotene, Phototherapy, RT	Remission
Patient 5	Endo et al.	46	M	Japanese	NR	CD3+, CD4+, CD8−, CD30−	CD3+, CD8+, granzyme B+, CD4−, CD30−	Match	Phototherapy	Stable Disease
Patient 6	Okada et al.	56	M	NR	IA	CD4+, CD8−, CD3+, CD5+, CD30−, granzyme B−	CD4−, CD8+, CD3+, CD5+, CD30−, granzyme B-	Match	Etretinate, Phototherapy, RT, CHEMOTHERAPY, allo-BMT	DOD
Patient 7	Kreuter et al.	72	M	White	IVA	CD4+, CD8−	CD8+, CD4-	Match	ECP, Bexarotene	DOD
Patient 8	Vargas Nevado et al.	84	M	NR	IB	CD2+, CD3+, CD4+, CD5+, CD7+, CD30+, CD8−, TIA-1−, Granzyme B−, CD56−	CD3+, CD5+, CD7+, βF1+, granzyme B+, TIA-1+, CD2−, CD4−, CD8−, CD30−, CD56−, CD20−, EBER−	Match	Topical corticosteroids and psoralen-UV-A	DOD
Patient 9	Johnson et al.	77	M	White	IIB	CD4+,CD3+, CD2+, CD5+, CD8−, CD20 partial+, CD30− Granzyme B+, TIA-1+	CD2+, CD3+, CD7+, CD8+, TIA-1+, granzyme B+, CD4−, CD5−, CD30−, ALK−, CD56−, EBER−, bF-1+	Match	Bexarotene, RT	DOD

Allo-BMT allogeneic bone marrow transplantation, *DOD* dead of disease, *ECP* extracorporeal photopheresis, *hyper-CVAD* hyperfractionated cyclophosphamide, vincristine, Adriamycin (doxorubicin), dexamethasone, *ICE* ifosfamide, carboplatin, etoposide, *MF* mycosis fungoides, *NR* not reported, *PCTCL* primary cutaneous T cell lymphoma, not otherwise specified, *RT* radiation therapy, *SZ* Sezary syndrome

mechanism and cause for this PS still remain a mystery. It is unclear if this occurrence is related to treatment, genetic alterations, tumor microenvironment, or chance. Also, it appears that PS in CTCL is infrequent, but it is important for the pathologist to keep this possibility in mind when assessing a potential recurrence of CTCL because, if proper care is not taken, the appropriate treatment may be delayed, or not pursued at all. In fact, many cases of CTCL are diagnosed based solely on morphology or minimal immunohistochemical stains. Therefore, it is likely that many cases with a PS have been overlooked. We hope that this report can increase awareness of the possibility of a PS in CTCL.

Compliance with ethical standards

All three authors made substantial contributions to the conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work. All authors participated in drafting the work and revising it critically for important intellectual content. All authors gave final approval of the version submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Cappelaere P (1998) Les lymphomes non hodgkiniens secondaires. Bull Cancer 85:217–231
2. Libra M, De Re V, Gasparotto D et al (2002) Differentiation between non-Hodgkin's lymphoma recurrence and second primary lymphoma by VDJ rearrangement analysis. Br J Haematol 118: 809–812
3. Pui CH, Raimondi SC, Head DR et al (1991) Characterization of childhood acute leukemia with multiple myeloid and lymphoid markers at diagnosis and at relapse. Blood 78:1327–1337
4. Leung W, Ribeiro RC, Hudson M, Tong X, Srivastava DK, Rubnitz JE, Sandlund JT, Razzouk BI, Evans WE, Pui CH (2001) Second malignancy after treatment of childhood acute myeloid leukemia. Leukemia. 15(1):41–45
5. Marks E, Shi Y, Wang Y (2017 Jul) CD117 (KIT) is a useful marker in the diagnosis of plasmablastic plasma cell myeloma. Histopathology. 71(1):81–88
6. Bradford PT, Devesa SS, Anderson WF, Toro JR (2009) Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 113:5064–5073
7. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, Robson A, Calonje E, Stefanato CM, Wain EM, Wilkins B, Fields PA, Dean A, Webb K, Scarisbrick J, Morris S, Whittaker SJ (2010) Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 28:4730–4739
8. Aung PP, Climent F, Muzzafar T, Curry JL, Patel KP, Servitje O, Prieto VG, Duvic M, Jaffe ES, Torres-Cabala CA (2014) Immunophenotypic shift of CD4 and CD8 antigen expression in primary cutaneous T-cell lymphomas: a clinicopathologic study of three cases. J Cutan Pathol 41(1):51–57
9. Endo C, Naka Y, Miyagaki T, Fujita H, Sugaya M, Kawashima M, Tsunemi Y (2016) Immunophenotypic shift from CD4+ to CD8+ in mycosis fungoides. Br J Dermatol 175:830–833
10. Okada S, Nannya Y, Ota S, Takazawa Y, Yamamoto G, Kumano K, Izutsu K, Takahashi T, Chiba S, Kurokawa M (2010) Cutaneous T-cell lymphoma (mycosis fungoides) relapsed with different immunological phenotype after bone marrow transplant. Br J Dermatol 162:229–230
11. Kreuter A, Altmeyer P (2005) Rapid onset of CD8+ aggressive T-cell lymphoma during bexarotene therapy in a patient with Sézary syndrome. J Am Acad Dermatol 53:1093–1095
12. Vargas Nevado Á, López Navarro N, Gallego Domínguez E, Herrera Ceballos E (2016) Immunophenotypic shift associated with Angiocentricity and Cytoxic characteristics in a case of mycosis Fungoides. Actas Dermosifiliogr 107(8):697–699
13. Johnson WT, Leeman-Neill RJ, Patel P, Ho J, Grandinetti LM, Jedrych J, Craig FE (2016) Fatal case of primary cutaneous aggressive T-cell lymphoma switching from a CD4+ to a CD8+ phenotype: progressive disease with Bexarotene and Romidepsin treatment. Am J Dermatopathol 38(11):832–837
14. Guitart J, Kennedy J, Ronan S, Chmiel JS, Hsiegh YC, Variakojis D (2001) Histologic criteria for the diagnosis of mycosis fungoides: proposal for a grading system to standardize pathology reporting. J Cutan Pathol 28(4):174–183
15. Patel KP, Pan Q, Wang Y, Maitta RW, Du J, Xue X, Lin J, Ratech H (2010) Comparison of BIOMED-2 versus laboratory-developed polymerase chain reaction assays for detecting T-cell receptor-gamma gene rearrangements. J Mol Diagn 12(2):226–237
16. Dewar R, Andea AA, Guitart J, Arber DA, Weiss LM (2015) Best practices in diagnostic immunohistochemistry: workup of cutaneous lymphoid lesions in the diagnosis of primary cutaneous lymphoma. Archives of Pathology & Laboratory Medicine 139(3): 338–350
17. Song SX, Willemze R, Swerdlow SH, Kinney MC, Said JW (2013) Mycosis Fungoides: report of the 2011 Society for Hematopathology/European Association for Haematopathology Workshop. Am J Clin Pathol 139(4):466–490
18. Nikolova M, Echchakir H, Wechsler J, Boumsell L, Bensussan A, Bagot M (2003) Isolation of a CD8alphaalpha+ CD4- tumour T-cell clone with cytotoxic activity from a CD4+ CD8- cutaneous T-cell lymphoma. Br J Dermatol 148(1):24–29
19. Washington LT, Huh YO, Powers LC, Duvic M (2002) Jones D. a stable aberrant immunophenotype characterizes nearly all cases of cutaneous T-cell lymphoma in blood and can be used to monitor response to therapy. BMC Clin Pathol 2(1):5
20. Agbay RL, Torres-Cabala CA, Patel KP et al (2017) Immunophenotypic shifts in primary cutaneous γδ T-cell lymphoma suggest antigenic modulation: a study of sequential biopsy specimens. Am J Surg Pathol 41(4):431–445
21. Guitart J, Martinez EME (2016) γδ T-cell in cutaneous and subcutaneous lymphoid infiltrates: malignant or not. J Cutan Pathol 43(12):1242–1244
22. Merrill ED, Agbay R, Miranda RN, Aung PP, Tetzlaff MT, Young KH, Curry JL, Nagarajan P, Ivan D, Prieto VG, Medeiros LJ, Duvic M, Torres-Cabala CA (2017) Primary cutaneous T-cell lymphomas showing Gamma-Delta (γδ) phenotype and predominantly Epidermotropic pattern are Clinicopathologically distinct from classic primary cutaneous γδ T-cell lymphomas. Am J Surg Pathol 41(2):204–215
23. Virmani P, Myskowski PL, Pulitzer M (2016) Unusual variants of mycosis fungoides. Diagn Histopathol (Oxf) 22(4):142–151
24. Vega F, Luthra R, Medeiros LJ et al (2002) Clonal heterogeneity in mycosis fungoides and its relationship to clinical course. Blood. 100(9):3369–3373

25. Boumsell L, Schmid M, Dastot H, Gouttefangeas C, Mathieu-Mahul D, Bensussan A (1990) In vitro differentiation from a pluripotent human CD4+CD8+ thymic cloned cell into four phenotypically distinct subsets. J Immunol 145(9):2797–2802
26. Sokol L, Loughran TP Jr (2003) Large granular lymphocyte leukemia and natural killer cell leukemia/lymphomas. Curr Treat Options in Oncol 4(4):289–296
27. Haydu JE, Ferrando AA (2013) Early T-cell precursor acute lymphoblastic leukaemia. Curr Opin Hematol 20(4):369–373