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Progression of undiagnosed cutaneous lymphoma after anti-tumor necrosis factor alpha therapy

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Abstract

Background—Cutaneous lymphoma (CL) diagnosed after anti-tumor necrosis factor (TNF)α therapy has been reported in the literature, yet a clear link between both events remains elusive.

Objective—To review our experience with CL diagnosed during or after the use of anti-TNFα therapies.

Methods—This is a multicenter retrospective study and a literature review.

Results—Twenty-two cases, including 20 cutaneous T-cell lymphomas (CTCL) and 2 cutaneous B-cell lymphomas (CBCL), were identified. In the CTCL group, 75% of the patients received an anti-TNFα agent for a presumed inflammatory skin condition. Mycosis fungoides and Sézary syndrome were the most common subtypes of CTCL diagnosed. Advanced disease (IIB – IVA) was commonly seen at time of diagnosis requiring aggressive therapy, including stem cell transplant in three patients. Two patients diagnosed with CBCL had an indolent course. A total of 31 cases were gathered from a literature search.

Limitations—This is a retrospective study.

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Conclusions—Our findings suggest that most of the identified patients were misdiagnosed as having psoriasis or eczema; therefore, a comprehensive morphological and molecular review of skin biopsies and peripheral blood should be considered prior to initiation of anti-TNFα therapy in patients with poorly defined dermatitis or atypical presentations of “psoriasis”.

Keywords

anti-tumor necrosis factor alpha agents; cutaneous lymphoma; immunosuppression; large cell transformation; psoriasiform dermatitis; spongiotic dermatitis

Introduction

Cutaneous lymphomas (CL) are rare cancers characterized by proliferation of malignant T or B-lymphocytes in the skin. Cutaneous T-cell lymphomas (CTCL) are more common than B-cell lymphomas, with mycosis fungoides (MF) being the most common subtype. The initial presentation of MF can mimic inflammatory skin conditions such as eczema, pigmented purpura, pityriasis lichenoides chronica, and psoriasis. This mimicry of benign dermatoses is a major challange for clinicians and pathologists that can lead to misdiagnosis and to the use of potentially harmful immunosuppressive agents in these patients.

Additionally, there is an increased risk of lymphoma with chronic use of immunosuppressive therapy such as cyclosporine, mercaptopurine, or anti-tumor necrosis factor (TNF)α agents, yet the effects of these agents on CL remains controversial.[1, 2] Approximately 30 cases of CL arising after anti-TNFα therapy have been reported in the literature.[1, 3–20] Some of those cases were eventually diagnosed as MF resembling psoriasis or eczema, with an unmasking of the lymphoma after receiving the anti-TNFα agent. Herein, we describe our multi-institutional set of patients diagnosed with cutaneous lymphomas after being exposed to anti-TNFα therapy.

Materials and methods

This is a case series derived from a multicenter retrospective chart review. Upon Institutional Review Board approval, patients diagnosed with CL after therapy with anti-TNFα agents were included. A literature search of case series and case reports with the same inclusion criteria was also performed. Clinical data were collected from the electronic medical records system, including gender, race, age of diagnosis of CL, disease for which the anti-TNFα agent was prescribed, other immunosuppressive treatment received, type of anti-TNFα agent received, time since anti-TNFα therapy was started until CL diagnosis, type of CL diagnosed, blood parameters at diagnosis such as lactate dehydrogenase (LDH), flow cytometry of peripheral blood, Sézary cell count, T-cell receptor (TCR) gene rearrangement in the blood and skin, initial TNM for non-MF/Sézary syndrome (SS) cases or TNMB staging for MF/SS cases, treatment received for CL, and outcome. Follow-up was assessed from diagnosis to the most recent point in time for which adequate patient data existed. Skin biopsies performed prior to and after receipt of anti-TNFα therapy were reviewed along with immunohistochemistry data, when available. Descriptive statistics including median (with range) were performed. The same data were also collected from published case series and case reports.

Results

A total of 22 patients, 15 male and 7 female, were included in the study. Twenty patients were diagnosed with CTCL and 2 with CBCL.

CTCL

Clinical, histologic, and therapeutic details of the 20 CTCL patients are reported in Table 1. The male-to-female ratio was 2:1, and the median age was 63 years (ranging from 21 to 76 years). Fifteen patients were White, 3 Black, and 2 Hispanic. A primary skin disorder was the indication for the use of anti-TNFα agents in 75% of patients. Most of these cases had been clinically diagnosed as psoriasis, psoriasiform dermatitis, or idiopathic erythroderma. Of the remaining 5 (25%) patients were diagnosed with rheumatoid arthritis (RA) in 2 patients, Crohn's disease (CD) in another 2 patients and sarcoidosis in one patient prior to use of anti-TNFα therapy. Of note, three of the five patients had a concomitant, but unspecified dermatitis prior to the initiation of the anti-TNFα agent.

Of the 18 patients with a skin disorder prior to anti-TNFα agent initiation, 15 had a skin biopsy performed. The most common histologic finding (46%) was "psoriasis" or "psoriasiform dermatitis" with some cases revealing striking similarity to psoriasis vulgaris including acanthosis, parakeratosis and exocytosis of neutrophils. Biopsies of the remaining 7 patients were reported as chronic spongiotic dermatitis, chronic lymphocytic dermatitis, or granulomatous dermatitis. We had the opportunity to retrospectively review 6 of these biopsies, which in some cases showed rare atypical lymphocytes but for the most part failed to fulfill histological or immunohistological criteria for CL. Only two patients with extensive skin disease had peripheral blood assessment performed before anti-TNFα therapy initiation. Both had an abnormal population of <200 cells, one by morphology and the other by flow cytometry, deemed clinically non-significant.

The median time from disease onset to initiation of anti-TNFα therapy was 6 years (ranging from 1 to 40 years). Thirteen patients received adalimumab, 6 etanercept, 4 infliximab, and 7 patients received more than 1 biologic agent. Fourteen patients received a median of 2 other immunosuppressive treatments prior to biologic agents, most commonly methotrexate and/or systemic steroids. A total of 3 patients had been treated with 6-mercaptopurine and/or azathioprine, and another one received cyclosporine A. Phototherapy had been given to 38% (5/13) of patients during their treatment course.

After anti-TNFα initiation, the majority of cases experienced worsening of skin disease, and three patients developed new skin eruptions. One of them was a 21-year-old patient with symmetrically distributed erythematous and scaly plaques, and biopsy-proven psoriasis, with a family history of psoriasis who developed *de novo* erythematous patches with a different distribution compared to his psoriasis (Case 9).

The median time from the start of anti-TNFα agent to CTCL diagnosis was 6 months (ranging from 1 to 24). Thirteen patients were diagnosed with MF, including 4 cases with the folliculotropic (FMF) variant, 2 patient with Sézary syndrome (SS), 3 patients with CTCL not otherwise specified (NOS), 1 patient with primary cutaneous aggressive

epidermotropic cytotoxic T-cell lymphoma (PCAEC-TCL), and 1 patient with primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL). Stages are detailed in Table 1. Limited blood involvement (B1 stage) was observed in 5 (45%) patients on blood smear and, 2 of which were confirmed by flow cytometry. One patient with CTCL NOS had an abnormal population of more than 3,000 cells, with a CD4-/CD8-null-phenotype that did not coincide with the phenotype of the atypical lymphocytes of the skin biopsy (Case 1). This patient died 2 months after the administration of the anti-TNFα agent from the CTCL.[21]

At diagnosis of CTCL, serum LDH was abnormal in 7 patients (70%), all of whom had advanced disease. Eighty-one percent of the patients had a T-cell clone present in the skin biopsy, and 58% had a T-cell clone present in peripheral blood. Same clonality in skin and blood was detected in one MF patient as well as the 2 patients with SS. Histological features and phenotype of the diagnostic skin biopsies are shown in Table 2. At the time of CTCL diagnosis, three biopsies consistent with MF showed features of large cell transformation (LCT), and large cell morphology was observed in one patient with CTCL NOS (Case 2).

The median time of follow-up for patients with available data (16 patients) was 25 months (ranging from 4 to 137). After discontinuation of the anti-TNFα agent, all patients received treatment according to their CTCL stage, except for one patient in whom subcutaneous nodules resolved spontaneously 7 months after the anti-TNFα agent was withdrawn (Case 3). Six patients achieved complete remission, 5 patients partial response, and 4 patients had no significant improvement with CTCL therapy. Three patients died from progressive disease (Table 1).

CBCL

One patient was a 29-year-old white man who presented with enlarged erythematous plaques on bilateral lower legs after 8 months on etanercept for RA. Skin biopsy showed features consistent with primary cutaneous marginal zone lymphoma (PCMZL) with Ig kappa light chain restriction and absence of Epstein-barr virus encoded RNA1 (EBER-1). Bone marrow biopsy was negative for lymphoma. After treatment with radiation, CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) and bortezomib, the patient achieved complete remission during a follow-up time of 3 years.

The second patient was a 53-year-old white man diagnosed with primary cutaneous follicular B-cell lymphoma (PCFL) after 1 month on adalimumab for psoriasis and psoriatic arthritis. This patient received methotrexate, phototherapy, and acitretin prior to biologic therapy. Etanercept was prescribed initially and after several years was switched to adalimumab to treat recalcitrant cutaneous psoriasis. Four weeks after this switch, he developed an erythematous plaque on the scalp, histologically consistent with PCFL with large cell morphology. Cells were positive for Bcl-6 and negative for MUM1, Bcl-2, and EBER-1. Bone marrow biopsy showed no evidence of involvement by lymphoma. After radiation, the patient achieved complete remission and was restarted on etanercept for psoriasis/psoriatic arthritis without recurrence of the PCFL at 9 years of follow-up.

Literature review (Table 3)—We identified 31 additional cases published in which CL was diagnosed after anti-TNFα agent exposure.[3, 5–7, 9–14, 16–20, 22–27] Twenty of these

previously published patients received an anti-TNFα agent for treatment of a systemic disease such as rheumatoid arthritis, inflammatory bowel disease, spondyloarthropathy, or psoriatic arthritis. Six of the 20 patients had a concurrent poorly characterized skin eruption. Eleven patients received an anti-TNFα agent for treatment of psoriasis, psoriasiform dermatitis, or non-specific dermatitis. Among the 17 patients with any type of dermatosis, over half either did not have a biopsy or had a biopsy with inconclusive results prior to anti-TNFα agent initiation. The median time on anti-TNFα agent until CL diagnosis was 5.5 months, ranging from 0.5 to 96 months. Nineteen patients were diagnosed with MF/SS, 3 of whom had the folliculotropic variant and 4 of whom had LCT. Cytotoxic lymphomas were diagnosed in 5 patients including subcutaneous panniculitis-like T-cell lymphoma, PC-GDTCL, dermal CD8+ T-cell lymphoma, and PCAEC-TCL. Two developed a CD30+ lymphoproliferative disorder. Other CLs were found in the remaining 5 patients including 2 with cutaneous Hodgkin's lymphoma, 2 with small/medium pleomorphic T-cell lymphoma, and 1 with chronic adult T-cell leukemia/lymphoma. Seventeen of the 19 patients with MF/SS had stage data available. Thirteen presented with early stage disease (IA or IB), 2 with stage IIB, and 4 with stage IVA. The median time of follow-up was 11 months (ranging from 0.7 to 19 months), and the majority of the patients achieved complete remission or partial response. Only one developed progressive disease from patch to tumor stage. Six patients died, mostly due to reasons unrelated to CL or due to CL treatment complications.

Discussion

We describe a cohort of patients with CL diagnosed after exposure to anti-TNFα agents. Compared to the cohort identified from the literature, a higher frequency of advanced disease was observed in our patient population. This difference might be explained by the inclusion criteria of the selected cohort. While our inclusion criteria considered all cases diagnosed with CL after anti-TNFα therapy, some case series specifically excluded patients misdiagnosed with psoriasis or eczema prior to use of biologic therapy. It is known that addition of immunosuppressive therapy in patients with CL often leads to disease progression.[20, 28] Our data underscore the risk of progression of previously undiagnosed CL when anti-TNFα therapy is used with the intent to treat a nonmalignant skin condition, likely due to the immunosuppressive properties of the treatment. Similar findings were observed in a recent publication that included CTCL cases exposed to any type of immunosuppression treatment, including cyclosporine, azathioprine, mycophenolate mofetil and anti-TNFα agents.[20]

Skin biopsies of the reported cases showed a high prevalence of LCT in biopsies with MF/SS, and large cell morphology in biopsies of other types of CL, consistent with our findings. This corroborates prior reports of aggressive histological features that indicate CL progression among patients given immunosuppressive therapy.[20, 28–31]

The rarity of CTCL relative to more common conditions like psoriasis and eczema combined with the fact that CTCL (most commonly MF) can clinically and histologically mimic these conditions increases the risk of misdiagnosis. In addition, a clinical diagnosis of psoriasis is often not confirmed with skin biopsy. It has been suggested that chronic lymphocyte-driven inflammatory states of psoriasis and atopic dermatitis plus the use of immunosuppressive

therapies may help to select a malignant T-cell clone, provoking the development of CTCL.[28, 32] Controversy surrounds the true prevalence of CL in patients with atopic dermatitis and psoriasis. One group reported a significant increased risk of CTCL in patients with moderate to severe psoriasis independent of the systemic therapy received (adjusted hazard ratio of 9.25 [CI: 95%]). Another group cites misdiagnosis of CTCL as eczema as a major confounding factor in reporting the true prevalence of CTCL in patients with atopic dermatitis.[33–35] We acknowledge the occasional difficulty in differentiating clinically and histologically between MF and psoriasis or eczema and have seen a similar situation with fatal disease progression in case 1 of this series. Indeed, MF/SS are known to occasionally require multiple skin biopsies for its diagnosis. Thus, close clinical monitoring and repeat biopsies with the use of immunohistochemistry and TCR gene rearrangement should be considered in ambiguous or atypical cases. In patients with extensive skin disease or erythroderma, flow cytometry and TCR gene rearrangement studies of peripheral blood can aid in diagnosis.[36]

There are no previous case reports in the literature of CBCL diagnosed during or after anti-TNFα therapy. It is difficult to definitively establish a causal relationship between the development of CL and the use anti-TNFα agents in our patients. However, the temporal association noted in the first case presented, in which erythematous plaques that were stable for 11 years enlarged with anti-TNFα therapy, suggests that adalimumab-induced immunosuppression can accelerate a previously quiescent low grade primary CL. The patient in the second case was treated with etanercept for several years, with PCFL appearing after 1 month of adalimumab therapy. After achieving complete remission, etanercept was re-started again without CL recurrence. Reinitiating anti-TNFα therapy after remission of CTCL is controversial, supported by only one case report of a patient with short-term follow-up.[22] Whether anti-TNFα agents can be safely restarted in patients with remission of a low grade CL requires further investigation. A balance between benefits and risks of using anti-TNFα therapy after a diagnosis of CL in patients with systemic diseases such as CD or RA must be carefully assessed.

Our series highlights a variety of CL presentations associated with anti-TNFα agents. Most cases had a preceding dermatitis that was possibly mistaken for psoriasis or eczema due to lack of definitive features of CTCL or early evolution of disease. The use of anti-TNFα therapy down-regulates innate and adaptive immunity that might normally control proliferation of malignant lymphocytes, thereby unmasking the lymphoma. This may explain why most of the patients in our series had a more advanced stage, often with large cell morphology or transformation at the time of diagnosis.

These findings underscore the need for all physicians prescribing anti-TNFα therapy to include a review of any cutaneous symptoms and a thorough skin exam prior to starting biologic therapy. A word of caution to avoid the use of anti-TNFα agents in erythrodermic patients in which there is any doubt of the psoriatic nature of the erythroderma has already been given. Moreover, the diagnosis must be reconsidered if erythroderma worsens after an anti-TNFα agent has been administered.[37] In selected cases, skin biopsy and specific peripheral blood studies such as flow cytometry and T-cell rearrangement, should be considered to exclude CL before initiating immunosuppressive therapies. In addition, close

monitoring and repeat biopsy of *de novo* skin eruptions or worsening of pre-existing dermatosis is strongly recommended in patients receiving any immunosuppressive therapy.

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ABBREVIATIONS

CBCL	Cutaneous b-cell lymphoma
CD	Crohn's disease
CL	cutaneous lymphoma
CTCL	Cutaneous t-cell lymphoma
EBER-1	Epstein-barr virus encoded RNA1
FMF	folliculotropic mycosis fungoides
LCT	large cell transformation
LDH	lactate dehydrogenase
MF	mycosis fungoides
NOS	not otherwise specified
PCAEC-TCL	primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma
PCFL	primary cutaneous follicular B-cell lymphoma
PCGD-TCL	primary cutaneous gamma-delta T-cell lymphoma
PCMZL	primary cutaneous marginal zone lymphoma
RA	rheumatoid arthritis
SS	Sézary syndrome
TCR	T-cell receptor
TNF	tumor necrosis factor

References

1. Mariette X, Tubach F, Bagheri H, et al. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010; 69(2):400–408. [PubMed: 19828563]
2. Mercer LK, Galloway JB, Lunt M, et al. Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis. 2016

3. Adams AE, Zwicker J, Curiel C, et al. Aggressive cutaneous T-cell lymphomas after TNFalpha blockade. J Am Acad Dermatol. 2004; 51(4):660–662. [PubMed: 15389210]
4. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006; 295(19):2275–2285. [PubMed: 16705109]
5. Chuang GS, Wasserman DI, Byers HR, et al. Hypopigmented T-cell dyscrasia evolving to hypopigmented mycosis fungoides during etanercept therapy. J Am Acad Dermatol. 2008; 59(5 Suppl):S121–122. [PubMed: 19119122]
6. Dalle S, Balme B, Berger F, et al. Mycosis fungoides-associated follicular mucinosis under adalimumab. Br J Dermatol. 2005; 153(1):207–208. [PubMed: 16029354]
7. Dauendorffer JN, Rivet J, Allard A, et al. Sezary syndrome in a patient receiving infliximab for ankylosing spondylitis. Br J Dermatol. 2007; 156(4):742–743. [PubMed: 17263820]
8. Imafuku S, Ito K, Nakayama J. Cutaneous pseudolymphoma induced by adalimumab and reproduced by infliximab in a patient with arthropathic psoriasis. Br J Dermatol. 2012; 166(3):675–678. [PubMed: 21910704]
9. Koens L, Senff NJ, Vermeer MH, et al. Cutaneous gamma/delta T-cell lymphoma during treatment with etanercept for rheumatoid arthritis. Acta Derm Venereol. 2009; 89(6):653–654. [PubMed: 19997706]
10. Lafaille P, Bouffard D, Provost N. Exacerbation of undiagnosed mycosis fungoides during treatment with etanercept. Arch Dermatol. 2009; 145(1):94–95. [PubMed: 19153359]
11. Lourari S, Prey S, Livideanu C, et al. Cutaneous T-cell lymphoma following treatment of rheumatoid arthritis with tumour necrosis factor-alpha blocking agents: two cases. J Eur Acad Dermatol Venereol. 2009; 23(8):967–968. [PubMed: 19192017]
12. Mahe E, Descamps V, Grossin M, et al. CD30+ T-cell lymphoma in a patient with psoriasis treated with ciclosporin and infliximab. Br J Dermatol. 2003; 149(1):170–173. [PubMed: 12890213]
13. Michot C, Costes V, Gerard-Dran D, et al. Subcutaneous panniculitis-like T-cell lymphoma in a patient receiving etanercept for rheumatoid arthritis. Br J Dermatol. 2009; 160(4):889–890. [PubMed: 19222452]
14. Nikolaou V, Papadavid E, Economidi A, et al. Mycosis fungoides in the era of antitumour necrosis factor-alpha treatments. Br J Dermatol. 2015; 173(2):590–593. [PubMed: 25639382]
15. Pallavicini FB, Caporali R, Sarzi-Puttini P, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev. 2010; 9(3):175–180. [PubMed: 19647103]
16. Quereux G, Renaut JJ, Peuvrel L, et al. Sudden onset of an aggressive cutaneous lymphoma in a young patient with psoriasis: role of immunosuppressants. Acta Derm Venereol. 2010; 90(6):616–620. [PubMed: 21057746]
17. Rojas-Feria M, Eslam M, Castro-Fernandez M, et al. Cutaneous lymphoma in a patient with ulcerative colitis after immunosuppressive therapy. J Crohns Colitis. 2011; 5(6):608–611. [PubMed: 22115382]
18. Sanli H, Ataman S, Akay BN, et al. Mycosis fungoides in a patient with ankylosing spondylitis during infliximab therapy. J Drugs Dermatol. 2007; 6(8):834–836. [PubMed: 17763616]
19. Vieites B, Avila R, Biscuola M, et al. Cutaneous Hodgkin-type lymphoproliferative lesion associated with immunomodulatory therapy for ulcerative colitis. J Cutan Pathol. 2011; 38(5):443–447. [PubMed: 21261674]
20. Foo SH, Shah F, Chaganti S, et al. Unmasking mycosis fungoides/Sezary syndrome from preceding or co-existing benign inflammatory dermatoses requiring systemic therapies: patients frequently present with advanced disease and have an aggressive clinical course. Br J Dermatol. 2016; 174(4):901–904. [PubMed: 26479768]
21. Martinez-Escala ME, Guitart J. Comments on ‘Generalized erythroderma and palmoplantar hyperkeratosis in a patient receiving TNF-alpha antagonist therapy’. J Cutan Pathol. 2015; 42(4): 295–296. [PubMed: 25354264]
22. Berthelot C, Cather J, Jones D, et al. Atypical CD8+ cutaneous T-cell lymphoma after immunomodulatory therapy. Clin Lymphoma Myeloma. 2006; 6(4):329–332. [PubMed: 16507211]

23. Bittencourt AL, Oliveira PD, Bittencourt VG, et al. Adult T-cell leukemia/lymphoma triggered by adalimumab. J Clin Virol. 2013; 58(2):494–496. [PubMed: 23911677]
24. Hruska CJ, Bertoli RJ, Young YD, et al. Primary cutaneous anaplastic large cell lymphoma in a patient receiving adalimumab. JAAD Case Rep. 2015; 1(2):56–59. [PubMed: 27051683]
25. Ma H, Qiu S, Lu R, et al. Methotrexate and etanercept-induced primary cutaneous CD4 positive small/medium-sized pleomorphic T-cell lymphoma. An Bras Dermatol. 2016; 91(3):368–371. [PubMed: 27438209]
26. Park JH, Lee J, Lee JH, et al. Lymphomatoid papulosis in a patient treated with adalimumab for juvenile rheumatoid arthritis. Dermatology. 2012; 225(3):259–263. [PubMed: 23257839]
27. Suga H, Sugaya M, Toyama T, et al. A case of mycosis fungoides with large cell transformation associated with infliximab treatment. Acta Derm Venereol. 2014; 94(2):233–234. [PubMed: 23975254]
28. Weenig RH, Comfere NI, Gibson LE, et al. Fatal cytotoxic cutaneous lymphoma presenting as ulcerative psoriasis. Arch Dermatol. 2009; 145(7):801–808. [PubMed: 19620563]
29. Corazza M, Zampino MR, Montanari A, et al. Primary cutaneous CD30+ large T-cell lymphoma in a patient with psoriasis treated with cyclosporine. Dermatology. 2003; 206(4):330–333. [PubMed: 12771475]
30. Fletcher CL, Orchard GE, Hubbard V, et al. CD30(+) cutaneous lymphoma in association with atopic eczema. Arch Dermatol. 2004; 140(4):449–454. [PubMed: 15096373]
31. Mougel F, Dalle S, Balme B, et al. Aggressive CD30 large cell lymphoma after cyclosporine given for putative atopic dermatitis. Dermatology. 2006; 213(3):239–241. [PubMed: 17033176]
32. Guitart J, Wood GS. On the trail of a new killer. Arch Dermatol. 2009; 145(7):811–813. [PubMed: 19620564]
33. Chiesa Fuxench ZC, Shin DB, Ogdie Beatty A, et al. The Risk of Cancer in Patients With Psoriasis: A Population-Based Cohort Study in the Health Improvement Network. JAMA Dermatol. 2016; 152(3):282–290. [PubMed: 26676102]
34. Gelfand JM, Shin DB, Neimann AL, et al. The risk of lymphoma in patients with psoriasis. J Invest Dermatol. 2006; 126(10):2194–2201. [PubMed: 16741509]
35. Legendre L, Barnetche T, Mazereeuw-Hautier J, et al. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: A systematic review and meta-analysis. J Am Acad Dermatol. 2015; 72(6):992–1002. [PubMed: 25840730]
36. Mangold AR, Thompson AK, Davis MD, et al. Early clinical manifestations of Sezary syndrome: A multicenter retrospective cohort study. J Am Acad Dermatol. 2017; 77(4):719–727. [PubMed: 28709694]
37. Zattra E, Belloni Fortina A, Peserico A, et al. Erythroderma in the era of biological therapies. Eur J Dermatol. 2012; 22(2):167–171. [PubMed: 22321651]

Capsule summary

- CL diagnosed after anti-TNFα therapy is most commonly associated with a misdiagnosis of “psoriasis”
- Anti-TNFα therapy can accelerate the CL course.
- Prior to initiating anti-TNFα therapy, skin biopsies and peripheral blood analysis should be considered in patients with atypical presentation of psoriasis in order to exclude a CL.

Table 1

Demographic, clinical and follow up data of patients diagnosed with CTCL.

Case	age/gender /race	Condition prior anti-TNFα agent (years)	Skin biopsy prior to anti-TNFα agent	Therapy prior to anti-TNFα agent	Anti-TNFα agents (months)	CTCL	Stage	Treatments	Outcome	F/u (months)
1[24]	69/F/B	Psoriasis (1)	Yes, psoriasiform dermatitis	MTX acitretin,MMF, P	Adalimumab (1)	CTCL NOS	T3N3M0	HDAC	DOD	7
2	63/M/W	Crohn's disease/Psoriasis (6 and 30 years)	Yes, inconclusive	NB-UVB	Adalimumab (1)	CTCL NOS	T3N2M0	PUVA, methotrexate, gemcitabine,NB-UVB	AWD	27
3	46/F/W	Crohn's disease (30)	N/A	6-MP, AZA	Adalimumab (8)	CTCL NOS	T2N0M0	Self-resolved	AWOD	33
4	72/M/W	Rheumatoid arthritis/dermatitis (uk and 6 years),	None	Leflunomide, sulfasalazine, AZA	adalimumab, etanercept, infliximab (UK)	FMF	IIB	Acitretin, XRT	AWD	12
5	29/F/B	Psoriasis (13)	Yes, N/A	MTX	Adalimumab,ustekinumab	FMF	IIB	INF, PUVA, BXT, HDAC, PXT, NM, TSEBT, FM, AHSCT	AWD	24
6	76/F/W	Psoriasis (20)	None	None	Etanercept (6)	FMF	IIB	MTX, GM, BXT	DOD	31
7	63/M/W	Psoriasis (3)	Yes, psoriasis	MTX	Etanercept (2)	FMF (LCT)	IIB	XRT, NB-UVB, acitretin, INF, BXT	AWD	26
8	72/F/W	Rheumatoid arthritis (40)	N/A	None	Etanercept (12)	MF	IA	NBUVB, MTX	AWOD	137
9	21/M/W	Psoriasis (UK)	Yes, psoriasis	None	Adalimumab (20)	MF	IA	NB-UVB, acitretin	AWD	27
10	64/F/W	Erythroderma (2)	Yes, chronic lymphocytic dermatitis	P, MTX, NB-UVB	Adalimumab, infliximab (UK)	MF	IIIA	ECP, DXR, MTX, NB-UVB, P, MOGA, HDAC, ALZ, AHSCT	AWOD	96
11	66/M/W	Eczema(since childhood)	None	MTX, NB-UVB, PUVA	Infliximab (UK)	MF	IIIA	TSEBT, HDAC, acitretin, GM, erlotinib, DXA, capecitabine	AWD	24
12	58/M/H	Psoriasis (2)	Yes, N/A	None	Adalimumab (4)	MF	IVA_2	XRT, PUVA, HDAC, NM	AWD	6
13	49/M/W	Psoriasis (40)	Yes, psoriasiform dermatitis	None	Adalimumab (24)	MF	IB	CHOEP, HDAC, BM, PTX, MTX.	AWOD	20
14	75/M/W	Erythroderma (5)	Yes, spongiotic dermatitis	Systemicsteroids	Adalimumab (UK)	MF (LCT)	IIIA	UK	Lost to f/u	UK
15	72/F/H	Eczema vs psoriasis(UK)	Yes, spongiotic dermatitis	Systemic steroids, NB-UVB	Apremilast, etanercept, adalimumab (UK)	MF (LCT)	UK	UK	Lost to f/u	UK
16	41/M/W	Erythroderma (9)	Yes, inconclusive	INF, NB-UVB, Thalidomide,AZA	Etanercept (8)	MF/LyPoverlap	IVA2	INF, DXR, DXA, GM, AHSCT	AWOD	137
17	27/M/B	Psoriaticarthritis/Psoriasis(1.5)	Yes, psoriasis	CsA, MTX	Adalimumab, ustekinumab (4)	PCAEC-TCL	T3N0MX	NBUVB, MTX, EPOCH, GM, HDAC, Brentuximab	DOD	13
18	42/M/W	Sarcoidosis (1.5)	Yes, granulomatous panniculitis	P, minocycline, hydroxicloroqui ne	Infliximab (1)	PC$\gamma\delta$TCL	T3NXM0	CHOEP, CsA, Brentuximab, AHSCT	AWOD	5
19	64/M/W	Psoriasis (4)	Yes, psoriasis	UK	Adalimumab, ustekinumab (24)	SS	IVA_1	ECP, BXT, INF	AWD	4
20	40/M/W	Psoriasis (7)	Yes, psoriasis	MTX, CSA	Apremilast, Adalimumab (UK)	SS	IVA_1	Acitretin, INF	AWD	3

6-MP: 6-mercaptopurine; ALZ: alemtuzumab; AWD: alive with disease; AWOD: alive without disease; AZA: azathioprine; BXT: bexarotene; CHOEP: etoposido, prednisone, vincristine, doxorrubicine; CsA: cyclosporine A; DOD: dead of disease; DXA: dexamethasone; ECP: photopheresis; EPOCH: etoposide, prednisone, vincristine, doxorubicin; f/u: follow-up; FM: fludarabine/melfalan; GM: gemcitabine; HDAC: histone deacetylase inhibitor (romidepsin); INF: interferon; MMF: mycofenolate mophetil; MOGA: mogalimumab; MTX:

methotrexate; N/A: non-available/non-applicable; NB-UVB: narrow band-ultraviolet; NM: nitrogen mustargen; P: prednisone; PUVA: psoralen-ultraviolet; PXT: praletexate; AHSCT: allogeneic hematopoietic stem cell transplant; TSEBT: total skin electron beam therapy; UK: unknown; XRT: radiation therapy.

Table 2

Immunohistochemical findings of CTCL diagnosis.

Case	Diagnosis	Main histological findings	CD2	CD3	CD4	CD5	CD7	CD8	CD30	TIA-1	EBER	BF1	GM1	CD4:CD8
1	CTCL NOS	Psoriasiform features with AL	N/A	+	+	+	+	−	N/A	10%	N/A	+	10%	8:1
2	CTCL NOS (large cells)	Spongiotic epidermis, superficial and mid dermis with AL	N/A	+	largecells	+	loss	-	10%	-	-	+	-	5:1
3	CTCL NOS	Lobular panniculitis with AL	−	+	−	−	−	−	−	+	−	+	−	4:1
4	FMF	Folliculotropism of AL	N/A	+	+	−	N/A	N/A	25%	N/A	N/A	+	−	10:1
5	FMF	Folliculotropism and syringotropism of AL		+	+		−	+	+			−	−	3: 1
6	FMF	Folliculotropism of AL, psoriasiform features	N/A	+	+	N/A	N/A	N/A	−	N/A	N/A	N/A	N/A	10:1
7	FMF (LCT)	Folliculotropism with AL, psoriasiform features, large cells	N/A	+	+	N/A	50%	−	+	−	N/A	N/A	N/A	10:1
8	MF	Band-like infiltrate with epidermotropism of AL		+	+	+	50%	−	N/A	N/A	−	N/A	N/A	5:1
9	MF	Band-like infiltrate with insterstitial AL	+	+	+	loss	loss	−				+	N/A	10:1
10	MF	Band-like infiltrate with epidermotropism of AL	N/A	+	+	+	N/A	N/A	few large cells	N/A	N/A	N/A	N/A	7:1
11	MF	Outside biopsy (N/A)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
12	MF	Band-like infiltrate with epidermotropism of AL	−	+	+	−	−	−	20%	−	−	−	−	6: 1
13	MF	Psoriasiform dermatitis with AL	N/A	+	+	+	−	−	N/A	N/A	N/A	+	N/A	4:1
14	MF (LCT)	Dense dermal infiltrate with syringotropism of large AL	-	+	+	+	-	-	10%	-	N/A	N/A	N/A	N/A
15	MF (LCT)	Dense dermal infiltrate with large AL	+	+	+	+	N/A	−	+		N/A	N/A	N/A	N/A
16	MF/LyP	Band-like infiltrate with epidermotropism of AL	+	−	+	−	+	−	50%	N/A	N/A	N/A	N/A	10:1
17	PCAEC-TCL	Dense intraepidermal infiltrate of AL	−	+	−	+	−	−	scattered	+	−	−	−	N/A
18	PCγδTCL	Patchy infiltrate of AL in dermis and lobular panniculitis	+	+	-	-	-	-	+	+	-	-	-	N/A
19	SS	Psoriasiform features with AL	N/A	+	+	N/A	N/A	−	N/A	N/A	N/A	N/A	N/A	10:1
20	SS	Psoriasiform features with AL	Few+	Few+	+	+	−	−	−	N/A	N/A	+	−	4:1

LCT: large cell transformation; N/A: non-available; AL: atypical lymphocytes

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Table 3

Comparison of demographics, clinical data, and outcomes between our cohort and literature cohort.

		Our cohort (n=22)	Literature cohort (n=31)
Male:Female		15:7	21:9, 1 not specified
Median age (range), ***years***		63 (21 – 72)	63 (28 – 75)
Disease for anti-TNFα agents	**Skin disease**	16	11
	Systemic disease *	6	20
Anti-TNFa used		Adalimumab (14), etanercept (7), infliximab (4)	Infliximab (12), etanercept (11), adalimumab (8)
Skin biopsy prior to anti-TNFα agent used		15/18 **	11/16 **
CL diagnosis (number of patients)		MF/SS (15), CTCL NOS (3), Cytotoxic CTCL (2), CBCL (2)	MF/SS (19), Cytotoxic CTCL (5), CD30 CLPD (2), cutaneous HD (2), SM PTCL (2), ATLL (1)
Disease stage in MF/SS patients (number of patients)		IA (2), IB (1), IIB (4), IIIA (2), IVA (4)	IA or IB (13), IIB (2), IVA (4)
Median time of follow-up (range), ***months***		25 (4 – 137)	11 (0.7 – 19)
Outcome (number of patients)		CR (9), PR (6), SD (3), PD (2)	CR (12), PR (9), SD (2), PD (1), Died (5)

* Crohn's disease, Rheumatoid arthritis, Spondyloarthropathy, psoriatic arthritis

** Skin biopsies/total of patients with skin disorder

TNFα: tumor necrosis factor alpha; MF: mycosis fungoides; SS: Sézary syndrome; CD30 CLPD: CD30 cutaneous lymphoproliferative disorder; SMPTCL: small/medium pleomorphic T-cell lymphoma; ATLL: adult T-cell lymphoma/leukemia, CR: complete remission; PR: partial response; SD: stable disease, PD: progressive disease.