Published in final edited form as:

J Am Acad Dermatol. 2018 March ; 78(3): 530–539. doi:10.1016/j.jaad.2017.09.015.

Unrelated immunodeficiency states may impact outcomes and immune-checkpoint molecule expression in patients with mycosis fungoides; a clinicopathologic case-control study

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Abstract

Background—Immunodeficiency (ID) correlates with worse outcomes and decreased immune-checkpoint molecule expression in melanoma. The impact of ID in mycosis fungoides (MF) is unknown.

Objective—Our goal was to evaluate the impact of ID in MF.

Methods—We conducted a case-control study of 17 MF patients with ID versus age/stage/race-matched controls, as a subset of a comparative analysis of 23 MF patients with ID (prior lymphoma, recent/current pregnancy, HIV, hypogammaglobulinemia, prior chemotherapy), versus without. PD-1, PD-L1, FoxP3, and IL-17 immunohistochemistry was performed on 12 ID patients and 10 controls.

Results—ID patients had more treatment failure (TF) (14/23 vs. 5/17, $p=0.028$), TF within 3-years of diagnosis (12/23 vs. 4/17, $p=0.050$), angiocentrism (6/12 vs. 0/10, $p=0.005$), larger cells (1.92 ± 0.51 vs. 1.30 ± 0.48 , $p=0.009$), cases with 10% PD-1 (9/11 vs. 4/10, $p=0.031$), PD-L1 positivity (7/12 vs. 2/10, $p=0.042$), and higher average percent PD-1+ cells (43.27 ± 40.22 vs. 11.2 ± 13.62 , $p=0.028$). No differences in survival, FoxP3, IL-17, histologic depth, ulceration, granulomatous changes or syringotropism were seen.

Limitations—This was a small single center study with heterogeneous immunodeficiencies.

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The other authors have no conflict of interest to declare.

The information presented here was previously presented as an oral presentation and in poster form at the ISCL/USCLC 3rd World Congress, NY, NY, October, 2016

The retrospective review was approved by the institutional review board of Memorial Sloan Kettering Cancer Center.

Conclusion—ID correlated with worse outcomes and increased PD-1 and PD-L1 in MF. MF patients with ID may be candidates for immune-checkpoint inhibitor therapy, pending further investigation.

Keywords

Immunocompromised host; immunosuppression; mycosis fungoides; programmed cell death 1 protein; peripheral tolerance; pregnancy; antineoplastic agent

Introduction

Blockade of the programmed death 1 (PD-1) pathway has proven to be a powerful therapeutic approach for many solid and hematological malignancies [1, 2]. Clinical trials of PD-1 inhibition in patients with cutaneous T-cell lymphomas (CTCL) [3, 4] are encouraging, however, treatment response is highly variable. New biomarkers to predict response to anti-PD1 therapy are necessary.

In patients with melanoma, the presence of tumor-infiltrating cytotoxic lymphocytes and elevated PD-1 and PD-L1 in the tumor microenvironment predict favorable responses to anti-PD-1 therapy [1, 5]. This inflamed phenotype is more likely to be identified in patients with immunogenic tumors e.g. with extensive carcinogenic damage, antigens from oncogenic viruses, and damage due to microsatellite instability [6, 7]. Differences in the underlying immune status of the patient may contribute to differences in tumor-associated immune cell infiltrates. For example, a recent study showed that melanoma patients with recent pregnancy—a state of selective immune-tolerance—had lower levels of tumor-infiltrating lymphocytes, lower PD-1 expression in the tumor microenvironment, and worse outcomes than non-pregnant counterparts [8]. Such findings suggest that cancers arising in the setting of pregnancy, and similarly other altered immunologic states, could be less susceptible to anti-PD-1 therapy.

In this context, we hypothesized that immunodeficiency is associated with poor outcomes and decreased PD-1 and PD-L1 expression in patients with mycosis fungoides (MF). We identified MF patients with a spectrum of unrelated immune dysregulated states, and compared them to a matched case control cohort for clinical features, histopathologic characteristics, and expression of PD-1 and PD-L1. We also compared FoxP3 and IL-17 expression, which were previously associated with immune dysregulation and cancer outcomes. [9–11]

Materials and Methods

A retrospective, case-control study was conducted with the approval of the Memorial Sloan Kettering Cancer Center (MSKCC) Institutional Review Board (WA0033-11). An MSKCC Darwin patient database search identified patients diagnosed with MF who also carried a diagnosis of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), primary immunodeficiency disorder (PID), pregnancy, or history of immunosuppressive chemotherapy from a prior malignancy (identified by diagnosis code and/or free text search). Diagnoses, as per International Society for Cutaneous Lymphoma guidelines [12], were

confirmed via review of available clinical, laboratory, and histopathology data. Age-, stage-, and sex-matched patients without immune alteration (one per test patient) were selected as controls.

Patient charts were reviewed and the following data was collected: age at MF diagnosis; sex; race/ethnicity; stage at diagnosis and last follow-up; highest LDH recorded; types and dates of other malignancies; history of immunotherapy for any condition; history of organ transplantation; history of collagen/vascular, autoimmune, atopic disease or allergies; and history of infections.

Given the indolent nature of MF, and good-prognosis bias in our younger patient cohort, we reasoned that outcome differences would manifest in treatment failures. Accordingly, history of treatment failure in the follow-up period and treatment failure within three years of diagnosis were selected as primary outcomes. Stage progression and all-cause mortality were evaluated as secondary outcomes. A treatment failure was defined as a change in treatment regimen due to unsatisfactory response. Changes in treatment regimen were not considered failure when due to medication intolerance alone.

H&E-stained slides from tumor specimens were evaluated for the following features: dermal involvement, subcutis involvement, spongiosis, epidermal hyperplasia, ulceration, syringotropism, angiocentrism, interface alteration, cell size (1, 2, or 3 for s, m, or l), and presence of eosinophils, neutrophils, plasma cells, and histiocytes. Large cell transformation, folliculotropism, and granulomatous disease were assessed via chart review.

Immunohistochemical studies were performed using antibodies against PD-1, PD-L1, IL-17, and FOXP3 proteins.

The percent of lymphocytic infiltrate staining positive for each marker was recorded for each specimen. Markers were evaluated as continuous variables (percent of infiltrate staining positive) and categorical variables (≥ 10% vs. <10% infiltrate staining positive).

Clinical and pathologic data of the two groups was compared using Barnard's test or two-sided Student's t-test for categorical and continuous variables, respectively. Because control patients were not identified for all test patients, statistical comparison of clinical data was performed twice for each variable – once including only matched immunodeficiency (ID) patients vs. controls and once including all ID patients vs. controls. Tissue was not available for all patients, so matched and unmatched ID patients were combined for statistical comparison of histopathological and immunohistochemical data against controls.

Results

ID patient characteristics

Twenty-three MF patients with ID were identified. Seven of twenty-three had recent/concurrent pregnancy, 1 had HIV, 1 had hypogammaglobulinemia secondary to a protein-losing-enteropathy, 1 had idiopathic CD4 cytopenia and hypogammaglobulinemia, 6 had history of prior chemotherapy including R-CHOP (1), CHOP (1), R-EPOCH (1), AC/Taxol (1), Taxol (1), and ABVD/MOPP (1). 11 had another lymphoma including CLL (6), DLBCL

(2), MZL (1), ALCL (1) and Hodgkin's lymphoma (1). Five patients had more than one condition (Table 1). Patient age ranged from 24 to 86 (median 44) years. Pregnant patients were younger (median age 31 years), and patients with lymphocytic malignancy were older (median age 53 years). At MF diagnosis, 19 patients were stage IA or IB, 1 was stage IIB, 2 were stage III, and 1 was stage IVA. Controls were identified for 17 of the 23 ID patients. Hereafter the ID patients with matched controls are referred to as "matched" ID patients, and the entire cohort of ID patients as "all" ID patients.

Clinical features of ID and control patients

Matched ID patients, all ID patients and control patients had similar mean age [49, 47 and 50 years], follow-up time (4, 5, and 4 years), and highest recorded LDH (295 U/L, 325 U/L and 301.6 U/L). (Table 2). The matched ID patients, all ID patients, and control patients had a similar gender breakdown (64.7, 65.2% and 64.7% female). There were no significant differences in history of erythroderma (17.6%, 13.0% and 17.6%), history of other malignancy (23.5%, 39.1% and 29.4%), history of collagen/vascular, or autoimmune disorders (23.5%, 17.4% and 11.8%), history of allergies or atopy (52.9%, 52.2% and 41.2%), or history of infection (HTLV, EBV, CMV, or HSV) (23.5%, 26.1% and 17.6%). History of immunotherapy (rituximab, ibrutinib, or interferon) was roughly 5 times as common in matched ID and all ID patients versus controls (29.4%, 21.7% and 5.9%). This difference was not statistically significant ($P=0.083$ and 0.143)

Treatment outcomes of ID and control patients

Results are shown in Table 3 and Figure 1. Matched ID patients and all ID patients were twice as likely to have treatment failure versus controls (58.8% and 69.9% vs. 29.4%, $P=0.050$ and 0.028). They were twice as likely to have treatment failure within 3 years of MF diagnosis versus control patients (58.8% and 52.2% vs. 23.5%, $P=0.023$ and 0.050). There were no significant differences between the average number of treatment failures, or the occurrence of stage progression or death between matched ID patients, all ID patients and control patients.

A subgroup analysis compared patients with lymphocytic malignancy ($n=11$) and patients with recent pregnancy ($n=7$) to control patients (Table 3 and figure 1). Patients with a history of lymphocytic malignancy were more likely to have treatment failure (63.6% vs. 29.4%, $P=0.046$) and trended toward increased treatment failure within 3 years of MF diagnosis (54.5% vs. 23.5%, $P=0.071$) versus control patients. There were no significant differences between the two groups in stage progression or deaths. There was a trend toward increased treatment failure within 3 years of MF diagnosis in patients with recent pregnancy (57.1% vs. 23.5%, $P=0.072$), but no difference in treatment failure overall, stage progression, or deaths.

Tumor histopathology in ID and control patients

Samples for histopathological analysis were available for 12 ID patients and 10 control patients (Table 4). ID patients were significantly more likely to exhibit angiocentric infiltrates (50% vs. 0%, $P=0.005$) and higher average lymphocyte size (1.92 ± 1.00 vs. 1.30 ± 0.48 , $P=0.009$) (Figure 2). Prevalence of the following features was not significantly

different between ID and control patients: large cell transformation, granulomatous infiltrate, folliculotropism, involvement of the dermis, or subcutis, epidermal hyperplasia, ulceration, spongiosis, and syringotropism. Presence of histiocytes, neutrophils, plasma cells, and eosinophils did not differ between ID and control patients.

PD-1, PD-L1, FoxP3, and IL-17 expression in tumors of ID and control patients

Samples for immunohistochemical analysis were available for 12 ID patients and 10 control patients. Subgroup analysis was performed for patients with lymphocytic malignancy (n=6) and patients with recent pregnancy (n=3) against controls for each marker (Table 4, Figure 2). The percent of infiltrate staining positive for PD-1 was significantly higher in ID patients (43.3 ± 40.2 vs. 11.2 ± 13.6 , $P=0.028$) (figure 4) and lymphocytic malignancy patients (67.0 ± 37.7 vs. 11.2 ± 13.6 , $P=0.025$) compared to controls, but there was no difference in patients with recent pregnancy and controls (12.0 ± 9.9 vs. 11.2 ± 13.6). There were no statistically significant differences between any groups in PD-L1, FoxP3, and IL-17 expression. ID patients were more likely to have 10% of infiltrate labeled for PD-1 (81.8% vs. 40.0%, $P=0.031$) and PD-L1 (58.3% vs. 20.0%, $P=0.042$) (figure 5), versus controls.

10% PD-1 positivity was more common in patients with lymphocytic malignancy (100% vs. 40%, $P=0.025$), but not 10% PD-L1 positivity (50% vs. 20%, $P=0.163$). There were no differences between any groups for 10% positivity of FoxP3 or IL-17 staining.

Discussion

MF is the most common CTCL and is characterized by a dysregulated proliferation of mature CD4+ T-cells. While typically an indolent disease, a subset of MF can involve extracutaneous sites including the lymph nodes and blood with poor prognosis [9]. Advanced stages of MF require more effective and targeted treatments with better, more reliable biomarkers that can predict response in order to improve survival.

The effectiveness of immune checkpoint inhibitors in other malignancies makes them an attractive option for advanced stage MF. High levels of PD-1 expression (over 50% lymphoid infiltrate) have been reported in up to 13% and 89% of MF and Sezary syndrome (SS) cases, respectively [13]. Moderate levels of PD-1 expression (over 30% of lymphoid infiltrate) were reported in up to 40% and 60% of plaque/patch- and tumor-stage MF cases, respectively [14]. These studies suggest that refractory or advanced stage MF may be sensitive to anti-PD-1 therapy. Several PD-1/PD-L1 blockade therapies are being evaluated in clinical trials for peripheral T-cell lymphomas (PTCL) such as CTCL. Preliminary results from one study evaluating nivolumab in patients with relapsed or refractory lymphoma showed that patients with MF and PTCL had overall response rates of 15% and 40% [3]. Initial results from another study evaluating pembrolizumab in patients with refractory MF or SS showed an objective response rate in 38% of treated patients with another 38% showing disease stability [15].

The positive response in some patients is promising. However, outcome variability complicates treatment decisions. Patients most suited to anti-PD-1 therapy seem to be those with an initial immune response to their tumors, which is subsequently quelled by upregulation of immune checkpoint molecules. Even in the absence of immune therapy, MF

patients are more likely to have a favorable clinical course when more CD8+ cytotoxic T-cells are present in their lesions [16, 17]. We reasoned that this initial immune response may be less likely in patients with underlying immune alteration, and hence MF patients with immune alteration may have a worse clinical course and be poor candidates for anti-PD-1 therapy.

In our series, MF patients with ID versus their immune-intact counterparts had similar rates of stage progression and death. However, ID patients had more treatment failure than immunocompetent patients. Overall, this is not surprising given the well-established association between various immunodeficiencies—including lymphomas—and cancer development and progression [18–20]. The association between pregnancy and cancer progression specifically is less well established and likely varies by cancer type. For example, there is evidence both for [21] and against [22] an association between pregnancy and poor outcomes in patients with melanoma. In another study, pregnancy was not associated with worse outcome in patients with various types of lymphoma [23]. In our patient cohort, patients with MF and recent pregnancy were nearly twice as likely to have treatment failure, but the result was not significant. Given the short length of follow-up, chronic nature of MF, and small subgroup sizes, our clinical outcome results should be interpreted with caution. A larger cohort of patients with longer follow-up is needed to confirm the effect of the various immunodeficiencies we examined on outcomes.

Of histologic features assessed, only angiocentrism and cell size were different between ID and control groups (Figure 3). ID cases were more likely to show >10% of cells expressing PD-1 and/or PD-L1, along with higher expression of PD-1. We suggest that the larger cell size of ID cases is due to alterations in cytoskeletal structure and cytoplasmic proteins within the exhausted PD-1 positive cells. Moreover, since the PD-1 positive cells cluster more around vascular structures (Figure 3, 4), the angiocentric pattern seen in ID associated MF may reflect the increased numbers of PD-1+ cells or their absence in lichenoid infiltrates. Histopathologic features historically associated with worse disease including depth, ulceration, granulomatous changes or syringotropism did not significantly differ between ID and control groups.

Contrary to our hypothesis, ID was associated with increased PD-1 and PD-L1 expression. However, analysis of subgroups showed that our results were similar to previous studies. Specifically, in our study the association of ID and PD-1 expression was most prominent in patients with lymphocytic malignancies, 60% of whom had CLL. Increased PD-1 expression in CLL patients compared to healthy patients has been demonstrated in previous studies [24, 25], and it is reasonable that this increase may persist when CLL patients develop MF. Additionally, while one study of pregnancy-associated melanoma showed decreased PD-1 expression compared to non-pregnant patients with melanoma [8], animal studies suggest that the PD-1/PD-L1 axis plays an important role in fetal tolerance [26, 27], and may be upregulated in pregnancy. In our study, patients with pregnancy-associated MF were more likely to have > 10% of lymphoid infiltrates express PD-1 and PD-L1, but this difference was non-significant, and the average PD-1 and PD-L1 expression in these patients was similar to control patients. Larger studies are needed to confirm the effect of pregnancy on PD-1/PD-L1 expression in patients with MF.

We studied the expression of FoxP3 and IL-17. FoxP3 is often expressed on non-malignant, tumor infiltrating regulatory T-cells (T-regs) in MF, and is associated with improved survival [11]. The survival benefit is thought to be due to downregulation of malignant T-cells by T-regs [28]. ID did not significantly alter FoxP3 expression in our study. While IL-17 has been shown to have both antitumor and protumor activity [29], a recent systematic review suggested IL-17 is primarily tumorigenic with only a subset of IL-17-producing Th17-cells showing tumor-suppressing effects [9]. The few studies that have examined IL-17 in MF have shown expression in some, but not all patients [30–32]. There was very low or absent IL-17 expression in our study, leaving the role of this cytokine unclear.

Overall, this study suggests that MF arising in the setting of altered underlying immune status may exhibit therapeutically relevant differences in pathogenesis than MF arising in patients with unaltered immunity. Specifically, patients with MF and ID may be good candidates for PD-1 inhibition. Larger studies stratified by type of ID are needed to clarify these results.

Acknowledgments

Funding sources: This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

Dr. Horwitz has consulting and/or research relationships with Celgene, Millenium Pharmaceuticals/Takeda, Kyowa-Hakka-Kirin, Forty-Seven, Seattle Genetics, Infinity Pharmaceuticals, HUYA, Spectrum Pharmaceuticals, ADCT therapeutics, Aileron Therapeutics

Dr. Moskowitz has research, speaking and advisory board relationships with BMS, Takeda and Seattle Genetics

References

1. Topalian SL, et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. *New England Journal of Medicine*. 2012; 366(26):2443–2454. [PubMed: 22658127]
2. Ansell SM, et al. PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma. *New England Journal of Medicine*. 2015; 372(4):311–319. [PubMed: 25482239]
3. Lesokhin AM, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. *J Clin Oncol*. 2016; 34(23):2698–704. [PubMed: 27269947]
4. Institute, N.C. Pembrolizumab in Treating Patients With Relapsed or Refractory Stage IB-IVB Mycosis Fungoides or Sezary Syndrome. 2014. <https://ClinicalTrials.gov/show/NCT02243579>
5. Tumeh PC, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014; 515(7528):568–71. [PubMed: 25428505]
6. Le DT, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *New England Journal of Medicine*. 2015; 372(26):2509–2520. [PubMed: 26028255]
7. Smyrk TC, et al. Tumor-infiltrating lymphocytes are a marker for microsatellite instability in colorectal carcinoma. *Cancer*. 2001; 91(12):2417–22. [PubMed: 11413533]
8. Mesinkovska, N., Ko, J. Worse Outcome in Melanoma Patients Recently Pregnant: Decreased T-Cell Programmed Death Receptor-1 (PD-1) Expression in Primary Tumors Suggests Immune Ignorance [Oral Presentation]. The American Society of Dermatopathology 51st Annual Meeting; Chicago, Illinois. 2014.
9. Punt S, et al. The correlations between IL-17 vs. Th17 cells and cancer patient survival: a systematic review. *Oncoimmunology*. 2015; 4(2):e984547. [PubMed: 25949881]
10. Nigam P, et al. Loss of IL-17-producing CD8 T cells during late chronic stage of pathogenic simian immunodeficiency virus infection. *J Immunol*. 2011; 186(2):745–53. [PubMed: 21148794]

11. Gjerdrum LM, et al. FOXP3+ regulatory T cells in cutaneous T-cell lymphomas: association with disease stage and survival. *Leukemia*. 2007; 21(12):2512–8. [PubMed: 17713545]
12. Olsen E, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. 2007; 110(6):1713–22. [PubMed: 17540844]
13. Cetinozman F, et al. Differential expression of programmed death-1 (PD-1) in Sezary syndrome and mycosis fungoides. *Arch Dermatol*. 2012; 148(12):1379–85. [PubMed: 23247480]
14. Wada DA, et al. Programmed death 1 is expressed in cutaneous infiltrates of mycosis fungoides and Sezary syndrome. *Am J Hematol*. 2011; 86(3):325–7. [PubMed: 21328438]
15. Khodadoust M, et al. Pembrolizumab for Treatment of Relapsed/Refractory Mycosis Fungoides and Sezary Syndrome: Clinical Efficacy in a Citn Multicenter Phase 2 Study. *Blood*. 2016; 128(22):181–181.
16. Hoppe RT, et al. CD8-positive tumor-infiltrating lymphocytes influence the long-term survival of patients with mycosis fungoides. *J Am Acad Dermatol*. 1995; 32(3):448–53. [PubMed: 7868714]
17. Vermeer MH, et al. CD8+ T cells in cutaneous T-cell lymphoma: expression of cytotoxic proteins, Fas Ligand, and killing inhibitory receptors and their relationship with clinical behavior. *J Clin Oncol*. 2001; 19(23):4322–9. [PubMed: 11731515]
18. Hersh EM, et al. Immunocompetence, immunodeficiency and prognosis in cancer. *Ann N Y Acad Sci*. 1976; 276:386–406. [PubMed: 800324]
19. Mueller BU, Pizzo PA. Cancer in children with primary or secondary immunodeficiencies. *J Pediatr*. 1995; 126(1):1–10. [PubMed: 7815195]
20. Travis LB, et al. Second cancers among long-term survivors of non-Hodgkin's lymphoma. *J Natl Cancer Inst*. 1993; 85(23):1932–7. [PubMed: 8230284]
21. Sutherland CM, et al. Effect of pregnancy upon malignant melanoma. *Surg Gynecol Obstet*. 1983; 157(5):443–6. [PubMed: 6314566]
22. Lens MB, et al. Effect of pregnancy on survival in women with cutaneous malignant melanoma. *J Clin Oncol*. 2004; 22(21):4369–75. [PubMed: 15514378]
23. Gelb AB, et al. Pregnancy-associated lymphomas. A clinicopathologic study. *Cancer*. 1996; 78(2):304–10. [PubMed: 8674008]
24. Grzywnowicz M, et al. Programmed death-1 and its ligand are novel immunotolerant molecules expressed on leukemic B cells in chronic lymphocytic leukemia. *PLoS One*. 2012; 7(4):e35178. [PubMed: 22532845]
25. Brusa D, et al. The PD-1/PD-L1 axis contributes to T-cell dysfunction in chronic lymphocytic leukemia. *Haematologica*. 2013; 98(6):953–63. [PubMed: 23300177]
26. Guleria I, et al. A critical role for the programmed death ligand 1 in fetomaternal tolerance. *J Exp Med*. 2005; 202(2):231–7. [PubMed: 16027236]
27. Taglauer ES, Yankee TM, Petroff MG. Maternal PD-1 regulates accumulation of fetal antigen-specific CD8+ T cells in pregnancy. *J Reprod Immunol*. 2009; 80(1–2):12–21. [PubMed: 19368976]
28. Krejsgaard T, et al. Regulatory T cells and immunodeficiency in mycosis fungoides and Sezary syndrome. *Leukemia*. 2012; 26(3):424–32. [PubMed: 21904385]
29. Ye J, Livergood RS, Peng G. The role and regulation of human Th17 cells in tumor immunity. *Am J Pathol*. 2013; 182(1):10–20. [PubMed: 23159950]
30. Ciree A, et al. Expression and activity of IL-17 in cutaneous T-cell lymphomas (mycosis fungoides and Sezary syndrome). *Int J Cancer*. 2004; 112(1):113–20. [PubMed: 15305382]
31. Miyagaki T, et al. IL-22, but not IL-17, dominant environment in cutaneous T-cell lymphoma. *Clin Cancer Res*. 2011; 17(24):7529–38. [PubMed: 22048239]
32. Chong BF, et al. Immune function abnormalities in peripheral blood mononuclear cell cytokine expression differentiates stages of cutaneous T-cell lymphoma/mycosis fungoides. *Clin Cancer Res*. 2008; 14(3):646–53. [PubMed: 18245523]

Capsule summary

- Immunodeficiency is associated with worse outcomes and decreased immune-checkpoint molecule expression in melanoma.
- We found that immunodeficient patients with mycosis fungoides had worse outcomes, and increased PD-1 and PD-L1 expression versus patients without immunodeficiency
- Immunodeficient patients with mycosis fungoides may be good candidates for immune-checkpoint inhibitor therapy.

Figure 1.

Graphic comparison of percentages of patients with mycosis fungoides with and without immunodeficiency, and with subsets of immunodeficiency, who had treatment failure, disease progression, and all-cause mortality. TF = any treatment failure; 3YR TF = treatment failure within 3 years of mycosis fungoides diagnosis; ID (n=23) = all immunodeficient patients; ID (n=17) = immunodeficient patients with matched controls; LM = subgroup of immunodeficient patients with lymphocytic malignancies.

Figure 2.
Histopathologic features of mycosis fungoides in immunodeficient and control patients. Infiltrates seen in biopsies from control patients with mycosis fungoides were dispersed (A, B), while immunodeficient patients showed more angiocentricity (C) and a higher average lymphocyte size (D).

Figure 3.

Graphic comparisons of percentages of lymphocytes (infiltrates) and of percentages of cases (patients) of mycosis fungoides with and without immunodeficiency, and with subsets of immunodeficiency, that show immunohistochemical labeling for PD-1, PD-L1, FOXp3 and IL-17. A: Overall percent of lymphoid infiltrate staining positive for each marker. B: Percent of patients with at least 10% of lymphoid infiltrate staining positive for each marker. ID = patients with immunodeficiency; LM = patients with lymphocytic malignancy.

Figure 4. Immunohistochemical staining for PD-1 in mycosis fungoides. A–C. Prominent labeling of mostly angiocentric (but also epidermotropic) infiltrates in immunocompromised patients with hypogammaglobulinemia, chronic lymphocytic leukemia, and marginal zone lymphoma post immunotherapy. D–F. Minimal PD-1 noted in control patients who show more prominently epidermotropic infiltrates.

Figure 5. Immunohistochemical staining for PD-L1 in mycosis fungoides patients with immunocompromise. A, B. PD-1 positive perivascular and interstitial dendritic mononuclear cells aggregate near angiocentric malignant lymphocytes.

Table 1

Presence of lymphoma, leukemia, pregnancy and/or chemotherapy and stage of mycosis fungoides at evaluation

	Immune alterations	Stage	Age	Sex
1	CLL	I	75	F
2	CLL	I	74	M
3	CLL	I	53	F
4	CLL	I	50	M
5	CLL	I	83	M
6	DLBCL, R-CHOP	III	86	M
7	MZL, R-EPOCH	IV	50	F
8	CLL, CHOP	I	62	M
9	DLBCL	II	47	F
10	ALCL	I	24	M
11	Hodgkin's, ABVD, MOPP	I	25	F
12	Pregnancy	I	32	F
13	Pregnancy	I	27	F
14	Pregnancy	I	27	F
15	Pregnancy	I	31	F
16	Pregnancy	III	37	F
17	Pregnancy	I	39	F
18	Pregnancy	I	29	F
19	HIV	I	43	M
20	HGG	I	48	F
21	HGG	I	44	M
22	AC, Taxol	I	62	F
23	Taxol	I	39	F

CLL chronic lymphocytic leukemia; DLBCL diffuse large B-cell lymphoma, R-CHOP rituximab, cyclophosphamide, vincristine and prednisone, MZL margin zone lymphoma, R-EPOCH CHOP plus etoposide phosphate, ALCL anaplastic large cell lymphoma, ABVD Adriamycin, bleomycin, vinblastine and doxorubicin, MOPP mechlorethamine, vincristine, procarbazine, prednisone, HIV human immunodeficiency virus, HGG hypo/agammaglobulinemia, F female, M male

Clinical features including prior immunotherapy, collagen vascular disease, viral exposure and atopy in mycosis fungoides patients with and without immunodeficiency

Table 2

	Matched ID only	All ID	Controls (n=17)	P-Value, Matched only vs. control	P-Value, all MF vs. control
Male sex	6/17 (35.3%)	8/23 (34.8%)	6/17 (35.3%)	1	0.551
Age at MF diagnosis	48.71 ± 19.857	47.26 ± 18.71	50 ± 17.74	0.841	0.64
Average MF stage at diagnosis	1.41 ± 0.94	1.37 ± 0.83	1.41 ± 0.94	1	0.82
Highest LDH	295 ± 208.24 (n=15)	325 ± 251.68 (n=18)	301.64 ± 273.13 (n=11)	0.947	0.82
History of erythroderma	3/17 (17.6%)	3/23 (13.0%)	3/17 (17.6%)	1	0.607
Alive at LFU	16/17 (94.1%)	21/23 (91.3%)	15/17 (88.2%)	0.46	0.697
Years of follow-up since MF diagnosis	3.88 ± 4.21	5.04 ± 5.68	4.18 ± 4.60	0.849	0.6
History of other malignancy	4/17 (23.5%)	9/23 (39.1%)	5/17 (29.4%)	0.458	0.376
Number of other malignancies	0.71 ± 1.53	0.78 ± 1.35	0.35 ± 0.61	0.387	0.18
History of immunotherapy	5/17 (29.4%)	5/23 (21.7%)	1/17 (5.9%)	0.083	0.143
Collagen, vascular, or autoimmune disease	4/17 (23.5%)	4/23 (17.4%)	2/17 (11.8%)	0.242	0.468
History of HTLV, hepatitis, EBV, CMV, or HSV infection	4/17 (23.5%)	6/23 (26.1%)	3/17 (17.6%)	0.528	0.344
History of atopy or allergy	9/17 (52.9%)	12/23 (52.2%)	7/17 (41.2%)	0.305	0.311

MF mycosis fungoides, LDH lactate dehydrogenase, LFU last follow-up, HTLV human T-lymphotropic virus, EBV Epstein Barr virus, CMV cytomegalovirus, HSV herpes simplex virus, vs. versus

Treatment failure, progression and mortality in mycosis fungoides patients with and without immunodeficiency with specific comparisons for lymphoid malignancy and pregnancy subsets

Table 3

	Matched ID only, P-value vs. control	All ID, P-value vs. control	Lymphocytic malignancy (n=11), P-value vs. control	Pregnancy (n=7), P-value vs. control	Controls (n=17)
Number of treatment failures	1.00 ± 1.22, P=0.419	1.13 ± 1.25, P=0.510	1.27 ± 1.27, P=0.653	1.00 ± 1.41, P=0.481	1.65 ± 3.00
Number of treatment failures within 3 years of MF diagnosis	0.76 ± 0.83, P=0.377	0.74 ± 9/2, P=0.360	0.82 ± 0.98, P=0.429	0.57 ± 0.535, P=0.264	1.47 ± 3.1
Any treatment failure	10/17 (58.8%), P=0.050	14/23 (60.9%), P=0.028	7/11 (63.6%), P=0.046	4/7 (57.1%), P=0.174	5/17 (29.4%)
Any failure within 3 years of MF diagnosis	10/17 (58.8%), P=0.023	12/23 (52.2%), P=0.050	6/11 (54.5%), P=0.071	4/7 (57.1%), P=0.072	4/17 (23.5%)
Patients with MF stage progression	3/17 (17.6%), P=1.000	4/23 (17.4%), P=0.577	2/11 (18.2%), P=0.572	1/7 (14.3%), P=0.584	3/17 (17.6%)
All-cause mortality	1/17 (5.9%), P=0.460	2/23 (8.7%), P=0.697	1/11 (9.1%), P=0.682	0/7 (0%), P=0.304	2/17 (11.8%)

MF mycosis fungoides

Table 4

Large cell transformation, folliculotropism, and other histopathologic features identified in biopsies from mycosis fungoides patients with and without immunodeficiency

	Immunocompromised	Controls	P-Value
Large cell transformation	2/23 (8.7%)	1/17 (5.9%)	0.653
Folliculotropism	4/23 (17.4%)	2/17 (11.8%)	0.468
Granulomatous disease	2/23 (8.7%)	0/17 (0%)	0.198
Dermal involvement	8/12 (67%)	8/10 (80%)	0.299
Spongiosis	4/12 (33%)	4/10 (40%)	0.403
Subcutis involvement	1/12 (8.3%)	0/10 (0%)	0.370
Epidermal hyperplasia	5/12 (41.7%)	4/10 (40%)	0.498
Ulceration	0/12 (0%)	0/10 (0%)	1.000
Syringotropism	2/12 (16.7%)	2/10 (20%)	0.561
Angiocentrism	6/12 (50%)	0/10 (0%)	0.005
Average lymphocyte size	1.92 ± 1.00	1.30 ± 0.48	0.009
Medium or large lymphocytes	10/12 (83.3%)	3/10 (30%)	0.007
Interface alteration	2/12 (16.7%)	4/10 (40%)	0.135
>5 eosinophils per HPF	2/12 (16.7%)	2/10 (20%)	0.561
Neutrophils present in infiltrate	1/12 (8.3%)	1/10 (10%)	0.715
Plasma cells present in infiltrate	2/12 (16.7%)	2/10 (20%)	0.561
Histiocytes present in infiltrate	3/12 (25%)	5/10(50%)	0.169
Large cell transformation	2/23 (8.7%)	1/17 (5.9%)	0.653

HPF high power field

Table 5

Comparison of immunohistochemical patterns for PD-1, PD-L1, FOXP3 and IL-17 in biopsies from mycosis fungoides patients with and without immunodeficiency with specific comparisons for lymphoid malignancy and pregnancy subsets

	Immunocompromised (n=12), P-value vs. controls	Lymphocytic malignancy (n=6), P-value vs. controls	Pregnancy (n=3), P-value vs. controls	Controls (n=10)
PD-1, percent of infiltrate	43.27 ± 40.22, P=0.028	67 ± 36.67, P=0.025	12.00 ± 9.85, P=0.915	11.2 ± 13.62
PD-1, patients with 10% infiltrate staining positive	9/11 (81.8%), P=0.031	5/5 (100%), P=0.025	2/3 (66.7%), P=0.291	4/10 (40%)
PD-L1, percent of infiltrate	9.00 ± 8.21, P=0.832	7.00 ± 6.01, P=0.661	8.33 ± 2.89, P=0.437	5.3 ± 10.66
PD-L1, patients with 10% infiltrate staining positive	7/12 (58.3%), P=0.042	3/6 (50%), P=0.163	2/3 (66.7%), P=0.156	2/10 (20%)
FoxP3, percent of infiltrate	11.53 ± 13.04, P=0.382	16.00 ± 16.21, P=0.744	11.67 ± 11.55, P=0.489	18.7 ± 21.91
FoxP3, patients with 10% infiltrate staining positive	4/12 (33.3%), P=0.143	3/6 (50%), P=0.416	1/3 (33.3%), P=0.291	6/10 (60%)
IL-17, percent of infiltrate	1.92 ± 1.56, P=0.719	1.00 ± 0.41, P=0.155	3.67 ± 2.31, P=0.365	2.1 ± 1.85
IL-17, patients with 10% infiltrate staining positive	0/11 (0%), P=1.000	0/6 (0%), P=1.000	0/3 (0%), P=1.000	0/10 (0%)