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CD4/CD8 double-negative mycosis fungoides: a review

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Abstract

Mycosis Fungoides (MF) stands as the predominant form of primary cutaneous T-cell lymphoma (CTCL). It manifests a diverse array of clinical, histological, and immunophenotypic variations, each bearing distinct prognostic implications. The typical immunophenotypic profile of mycosis fungoides involves CD3+/CD4+/CD45RO+ memory T cells. Notably, the CD4-/CD8- double-negative variant of MF is a rare occurrence, observed in approximately 12% of early-stage cases and more prevalent in tumor-stage instances, often correlated with atypical clinical presentations. Despite its rarity, scant information is available about double-negative Mycosis Fungoides, with only a limited number of cases documented in the existing literature. This review aims to provide enhanced clarity, comprehension, and a detailed exploration of the spectrum encompassing double-negative mycosis fungoides.

Introduction

Cutaneous T-Cell Lymphomas (CTCL) is the second most common extranodal non-Hodgkin's lymphomas following gastrointestinal lymphoma.[1] Mycosis Fungoides (MF) is a form of non-Hodgkin lymphoma that is considered the most common type of primary cutaneous T-cell lymphoma (CTCL). MF is a neoplasia of malignant monoclonal T lymphocytes that generally invades the skin and causes cutaneous signs and symptoms.[2-4] It is characterized clinically during early stages as erythematous scaly patches and plaques, or during advanced stages as tumors or erythroderma, with lymph node and/or visceral involvement.[5] And histologically presents as an epidermotropic infiltrate of small-medium sized CD4+ T lymphocytes with cerebriform nuclei.[2] Mycosis Fungoides (MF) is the most prevalent cutaneous T-cell lymphoma, accounting for 50-65% of cases. Typically seen in men (1.6-2:1) ratio and appears in late adulthood with 55-60 years as a median age of diagnosis.[2-4] Even so, MF is a rare and uncommon condition, the incidence of MF in the United States is approximately 0.3-1.02 new cases per 100.000/year.[6] MF follows an indolent clinical course over years, with an estimated 5-year survival rate of 87% and a median survival of 11.4 years.[7] Also patients who present with involvement of lymph nodes or viscera have a median survival of <1.5%.[8] MF natural history is a classical slow progression from patches to plaques to tumors stage typically on unexposed areas such as the trunk, buttocks and thighs.[9] Due to MF manifesting a variety of clinical and pathological presentations, atypical presentations of MF may be difficult to diagnose.[3] Within this broad spectrum of clinical presentations, the World Health Organization (WHO) classified MF into 3 main variants or subtypes; folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin.[10] MF displays a broad spectrum of clinical, histological and immunophenotypic variants with different prognostic impacts. The classic immunophenotype

expression of MF is CD3+/CD4+/CD45RO+memory T cells.[1] CD4-/CD8- double negative mycosis fungoides is a rare condition, observed in approximately 12% of early-stage MF and more commonly in tumor-stage, and appears to be associated with an unusual clinical presentation.[11]

Very little is known about double-negative MF and only a small number of cases are reported in the literature. Data on the clinical behavior and prognosis of different immunophenotypic variants remain limited. Better understanding of different MF immunophenotypes will improve patient management by predicting the transformation of the clinically irrelevant variants of MF and their variable clinical presentations, especially double-negative immunophenotypes. The aim of this review is to have a closer look into the spectrum of mycosis fungoides, collecting the data and providing a brief summary of novel cases of double-negative MF that were reported.

Materials and Methodology

The electronic database MEDLINE was searched through PUBMED and Google Scholar in July 2022 using the following search terms: *Mycosis Fungoides - MF - Cutaneous T-cell lymphomas - Double-negative - CD4/CD8 negative.*

Results

After applying the inclusion criteria, the search reveals a total of 42 cases of double-negative MF have been reported in the literature.[11-23] Herein, we summarize the findings in the literature in order from the oldest to most recent. Summary of the clinical data of each research is seen in **[Table1]**. Summary of Immunophenotype of intraepidermal atypical lymphocytes **[Table 2].**

Discussion

Mycosis Fungoides is the most common primary Cutaneous T-cell Lymphoma (CTCL) with a slow indolent clinical course that usually affects older adults (median age at diagnosis: 55-60 years; male-to-female ratio: 1.6-2:1)[2,24]. Our narrative review is a comprehensive compilation of double-negative CD4/CD8 MF cases reported in the literature. We have collected a total of 42 known cases of double-negative MF. The cases included 19 males, 15 females and 8 undocumented. The male-to-female ratio was (1.26:1) and the age at diagnosis ranged from (11 - 84) years of age. Eleven patients had classic MF and 16 with other clinical variants: hypopigmented in 7 patients, Localized in 3 patients, folliculotropic in 2 patients, ichthyosiform in one patient, purpuric in one patient, erythrodermic in one patient and erythema gyratum repens-like in one patient.Thirty-two cases were early stage at diagnosis (IA-IIA), and 7 cases were advanced stage. The clinical course was indolent except for advanced stage at diagnosis due to bone marrow and lymph node metastasis, liver metastasis and

large cell transformation (LCT) in cases 2, 4 and 5 respectively [12], frontal dural invasion in case 38[19], advanced erythrodermic MF in case 39,[20] pleural, lung and lymph node metastasis in case 40[21] and lung, leptomeningeal involvement and large cell transformation (LCT) in case 42.[23]

The classic histopathologic features of patch/plaque stage MF show a superficial bandlike or lichenoid infiltration of lymphocytes and histiocytes. Atypical cells are highly indented (cerebriform), small to medium sized and mostly confined to the dermis (epidermotropism). In cases of CD4/CD8 double-negative MF, histopathology is almost the same as conventional type.The classic immunophenotype expression of MF is CD3+/CD4+/CD45RO+memory T cells.[1] All 42 cases observed CD4/CD8 double-negative immunophenotype. Negative CD7 was observed in 28 (78%) out of 36 cases.CD45RO, a memory phenotype marker, was expressed in 20 (69%) of 29 cases and TIA-1, a cytotoxic marker, was expressed in 12 (63%) of 19 cases. CD56 was positively expressed in 2 (6%) of 33 cases and CD30 was positive in 7 (20%) out of 35 cases. MF can lose expression of both CD4 and CD8 during the progression of disease to tumor stage, one study expressed the classic MF CD4+/CD8- immunophenotype then became double-negative late in the disease.[23] Large cell Transformation (LCT) was observed in two cases.[12,23] A previous case series found that patients with LCT have a greater risk of CNS involvement compared to non-LCT [25], which likely explains the extracutaneous dissemination to the leptomeninges in case 42.[23] Cases of double-negative MF occasionally express cytotoxic markers such as TIA-1 and CD56 but clinical behavior do not differ from conventional MF.[26-28]

Our review summarized the cases of CD4/CD8 double-negative MF with their unique characteristics and unusual clinical presentations.The median age at diagnosis of Mycosis fungoides is usually 55–60 years[2,24], and the incidence of MF rises relatively with age.[29] Our review revealed a younger age at time of diagnosis (Mean: 48.9 years), (median: 46.5 years) and a smaller male-to-female ratio (1.26:2) than those with conventional MF. Clinico-pathological variability exhibited by MF renders cases to a later more advanced stage of diagnosis. Double-negative MF is a less common immunophenotypic variant with a greater potential in delaying the histopathologic diagnosis.Despite efforts to set a multifaceted criteria to establish diagnosis in more advanced stages[30], the PROCLIPI study conducted by Scarisbrick et al shows a 12-100 months delay in the overall diagnosis of MF.[31] We found that more recent cases of DN-MF progressed to extracutaneous dissemination such as visceral organ and lymph node involvement.Wilmas et al (Case 42) showed lung and leptomeningeal involvement.[23] Ruiz et al (Case 40) progressed to pleural effusion and left lung atelectasis which complicated to developing unresolving (culture negative) pneumonia that led to respiratory failure and eventual death.[21] Nasser et al (Case 39) presented with erythrodermic MF, was admitted to the ICU due to septic shock and died after 2 weeks of admission (1.5 months after his diagnosis).[20]

Haghayeghi et al (Case 38) showed frontal dural invasion.[19] Similar to what Willemze et al found, people with effaced lymph nodes, visceral involvement, transformation into large T-cell lymphoma (LCT) and ICU admission had an aggressive clinical course.[1] It is also noteworthy to mention Cho-Vega et al case report (case 33), the coexistence of MF and B-cell lymphoma, where they reported a case of early double-negative MF associated with cutaneous follicular center lymphoma in the same patient, which to our knowledge never been reported before.[14]

MF is considered incurable with some patients experiencing periods of remission. Double-negative immunophenotype typically demonstrates a behavior of rapid multifocal dissemination and resistance to multi-agent therapy.[23] In skin confined disease, skin-targeted therapies are preferred. Patients with early stage MF, topical steroids, PUVA, UVB, localized radiotherapy and interferon gamma can be used.[32,33] Patients with advanced stages or refractory cutaneous disease, systemic therapy such as treatment with retinoids, low dose Methotrexate or chemotherapy should be considered.[34,35] There is an increasing use of biologic therapy such as interferon alpha, traditional and new retinoids such as bexarotene and especially newer agents like anti-CCR4 humanized monoclonal antibody such as mogamulizumab may offer longer survival benefits in selected patients.[36-38] Our review of double-negative cases revealed diverse treatments, encompassing skin-directed therapies, corticosteroids, methotrexate, phototherapy, radiation, chemotherapy, and biologics. Special cases demanded tailored approaches, such as local radiation for extracutaneous dissemination and surgical excision for dural invasion. In the realm of treatment options, double-negative cases are treated similarly to classic MF. However, the timing of treatment initiation assumes significance, given the delayed diagnosis commonly associated with double-negative cases.

In conclusion, our comprehensive review delves into the unique characteristics and clinical presentations of CD4/CD8 double-negative Mycosis Fungoides (MF), a less common immunophenotypic variant with distinct features. We examined 42 reported cases, revealing a younger age at diagnosis and a smaller male-to-female ratio compared to conventional MF. Clinico-pathological variability often leads to delayed diagnoses and more advanced disease stages. Despite the incurable nature of MF, treatment approaches vary, with double-negative cases demonstrating rapid multifocal dissemination and resistance to multi-agent therapy. The diverse therapeutic strategies identified in our review underscore the need for tailored approaches, ranging from skin-directed therapies to systemic treatments. Notably, the delayed initiation of treatment in double-negative cases emphasizes the challenges associated with timely diagnosis. Our findings contribute to the understanding of this rare variant, providing insights into its clinical behavior and therapeutic considerations.

Conclusions

CD4/CD8 Double-negative Mycosis Fungoides is a rare condition that usually presents with an unusual clinical presentation which makes the diagnosis quite challenging. High index of suspicion and clinicopathological correlation is always required when encountering patients with possible MF, as it is important to consider unusual variants such as CD4/CD8 double -negative variant. Physicians should also be aware of the factors and red flags that are associated with poor prognosis and survival such as clinically advanced stage at diagnosis, large cell transformation (LCT), extracutaneous disease involvement, age greater than 60 and ICU admission.

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Table 1. Summary of the clinical data.

Study	Case	Age (Y)/ Gender	Duration of disease	Clinical subtype	Stage at diagnosis	Treatment	Other organ involvement	Prognosis and survival (Y)
Fierro MT Et al.[12]	1	72/ M	NA	NA	Plaque	PUVA,etretinate and chemotherapy	NA	CR
	2	77/F	NA	NA	Tumor	PUVA, X-ray and chemotherapy	Lymph node/ bone marrow	Death
	3	52/F	NA	NA	Tumor	PUVA	NA	PR
	4	82/F	NA	NA	Tumor	PUVA, X-ray and chemotherapy	Liver	Death
	5	NA	NA	NA	IIB	Chemotherapy	Large Cell Transformation (LCT)	Death
	6	NA	NA	NA	IA/IB	PUVA/X-ray /IFNα	NA	Indolent course
	7	NA	NA	NA	IA/IB	PUVA/X-ray /IFNα	NA	Indolent course
	8	NA	NA	NA	IA/IB	PUVA/X-ray	NA	Indolent course

						/IFNα		
	9	NA	NA	NA	IA/IB	PUVA/X-ray /IFNα	NA	Indolent course
	10	NA	NA	NA	IA/IB	PUVA/X-ray /IFNα	NA	Indolent course
	11	NA	NA	NA	IA/IB	PUVA/X-ray /IFNα	NA	Indolent course
	12	NA	NA	NA	IA/IB	PUVA/X-ray /IFNα	NA	Indolent course
Hodak Et al.[11]	13	77/ M	3 years	Classic	IB	Skin target therapy	NA	Indolent course
	14	12/ M	5 years	Hypopigmented	IB	Skin target therapy	NA	Indolent course
	15	38/F	4 years	Hypopigmented	IB	Skin target therapy	NA	Indolent course
	16	11/ M	9 years	Hypopigmented	IB	Skin target therapy	NA	Indolent course
	17	45/ M	4 years	Localized/Unilesional	Patch	Skin target therapy	NA	Indolent course
	18	72/ M	15 years	Classic	IA	Skin target therapy	NA	Indolent course

	19	71/F	0.5 years	Classic	IB	Skin target therapy	NA	Indolent course
	20	61/F	10 years	Classic	IA	Skin target therapy	NA	Indolent course
	21	28/ M	2 years	Classic	IB	Skin target therapy	NA	Indolent course
	22	55/ M	10 years	Classic	IB	Skin target therapy	NA	Indolent course
	23	47/ M	20 years	Classic	IA	Skin target therapy	NA	Indolent course
	24	73/F	10 years	Localized/Unilesional	Plaque	Skin target therapy	NA	Indolent course
	25	14/F	10 years	Hypopigmented	IA	Skin target therapy	NA	Indolent course
	26	27/ M	9 years	Classic	IB	Skin target therapy	NA	Indolent course
	27	14/ M	12 years	Hypopigmented	IB	Skin target therapy	NA	Indolent course
	28	14/ M	8 years	Ichthyosiform	IB	Skin target therapy	NA	Indolent course
	29	34/F	1 year	Localized/Pagetoid	Plaque	Skin target therapy	NA	Indolent course

				reticulosis				
	30	34/ M	2 years	Classic and Purpuric	IB	Skin target therapy	NA	Indolent course
Massone C Et al.[13]	31	23/F	NA	NA	NA	NA	NA	NA
	32	45/F	NA	NA	NA	NA	NA	NA
Cho-vega JH Et al. [14]	33	84/ M	Few weeks	Classic	NA	Skin target therapy	Primary cutaneous follicular center lymphoma	PR
Kempf W Et al.[15]	34	70/F	5 years	Hypopigmented	IB	NBUVB	NA	PR
Nagase K Et al.[16]	35	73/ M	10 years	Erythema gyratum repens-like	IB	PUVA	NA	PR
Ito A Et al.[17]	36	55/F	30 years	Hypopigmented	II B	NBUVB	NA	Indolent course
Shon U Et al.[18]	37	41/ M	3 years	Classic	NA	Refused treatment	NA	Indolent course
Haghayeghi K Et al.[19]	38	43/F	15 years	Classic	IIB		Frontal dural invasion	PR

						CHOEP/ Radiation therapy/ Total skin electron beam therapy		
Alnasser MA Et al.[20]	39	60/ M	5 years	Erythrodermic	IIIA	Oral prednisolone & cyclosporine	NA	Death
Kasinathan G Et al.[21]	40	46/ M	1 year	Folliculotropic	NA	local radical radiotherapy/ CHOEP and IFNα	Pleura/Lungs/Lymph nodes	Death
Ballano Ruiz A Et al.[22]	41	42/ M	2 years	Pagetoid reticulosis	NA	Methotrexate/ NBUVB/ phototherapy	NA	Indolent course
Wilmas KM Et al.[23]	42	71/F	22 years	Folliculotropic	IVB	Skin target therapy/PUVA/ phototherapy/ Local radiation	Lungs/Leptomeninges/ Large Cell Transformation (LCT)	Indolent course

Abbreviations used: CHOEP, cyclophosphamide, hydroxydaunorubicin, oncovin, etoposide, prednisone; CR, complete response; F, female; IFN, interferon; M, male; MF, mycosis fungoides; NA, not applicable; NBUVB, narrow-band ultraviolet B; PR, partial response; PUVA, psoralen ultraviolet A; Y, years.

Table 2. Immunophenotype of intraepidermal atypical lymphocytes.

Study	Case	CD3	CD4	CD8	CD7	CD45RO	TIA-1	CD56	CD30	TCR-β	TCR-δ
Fierro MT Et al.[12]	1	+	–	–	NA	NA	NA	NA	+	+	–
	2	+	–	–	+	NA	NA	NA	–	+	–
	3	+	–	–	–	NA	NA	NA	–	+	–
	4	+	–	–	–	NA	NA	NA	–	–	+
	5	3+	–	–	2+	–	NA	2+	–	3+	–
	6	3+	–	–	–	2+	NA	–	–	3+	–
	7	3+	–	–	–	–	NA	–	2+	–	3+
	8	–	–	–	–	2+	NA	–	2+	3+	–
	9	3+	–	–	2+	–	NA	2+	2+	–	–
	10	3+	–	–	–	–	NA	–	–	–	3+
	11	3+	–	–	2+	–	NA	–	2+	–	3+
	12	3+	–	–	2+	–	NA	–	–	3+	–
Hodak Et al. [11]	13	3+	–	–	–	3+	3+	–	–	2+	–
	14	3+	–	–	–	3+	3+	3+	–	2+	–
	15	3+	–	–	–	3+	–	–	–	–	–

	16	3+	–	–	–	–	3+	–	–	NA	NA
	17	3+	–	–	–	3+	NA	–	–	–	–
	18	3+	–	–	–	3+	–	–	–	–	1+
	19	3+	–	–	–	3+	–	–	–	3+	–
	20	3+	–	–	–	3+	3+	–	–	–	–
	21	3+	–	–	–	3+	3+	–	–	2+	–
	22	3+	–	–	–	3+	3+	–	–	–	–
	23	3+	–	–	–	3+	NA	–	–	2+	1+
	24	3+	–	–	–	3+	3+	–	1+	–	3+
	25	3+	–	–	–	3+	3+	–	–	NA	NA
	26	3+	–	–	–	3+	3+	–	2+	–	–
	27	3+	–	–	–	3+	3+	–	–	–	1+
	28	3+	–	–	NA	NA	NA	NA	NA	1+	–
	29	3+	–	–	–	NA	NA	NA	NA	3+	–
	30	3+	–	–	–	3+	1+	–	–	3+	–
Massone C Et al.[13]	31	NA	–	–	NA	NA	–	–	NA	+	NA
	32	NA	–	–	NA	NA	–	–	NA	+	NA

Cho-vega JH Et al.[14]	33	+	–	–	–	NA	–	–	NA	NA	NA
Kempf W Et al.[15]	34	3+	–	–	3+	–	–	–	–	–	–
Nagase K Et al.[16]	35	+	–	–	NA	+	NA	NA	NA	NA	NA
Ito A Et al.[17]	36	3+	–	–	–	3+	–	–	–	+	NA
Shon U Et al.[18]	37	+	–	–	–	+	–	–	+	NA	NA
Haghayeghi K Et al.[19]	38	+	–	–	+	NA	NA	–	–	-/+	–
Alnasser MA Et al.[20]	39	+	–	–	–	+	NA	NA	NA	NA	NA
Kasinathan G Et al.[21]	40	+	–	–	+	NA	–	–	–	+	–
Ballano Ruiz A Et al.[22]	41	+	–	–	–	–	+	–	–	–	NA
Wilmas KM Et al.[23]	42	+	–	–	–	NA	NA	NA	–	NA	NA

Abbreviations used: NA, not applicable; TCR, T-cell receptor; TIA-1, T-cell-restricted intracellular antigen; w, weak staining; (–) , < 10% cells positive; (1+), < 25% cells positive; (2+), < 50%cells positive; (3+), > 50% cells positive.