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Incidence of γδ phenotype in mycosis fungoides: a prospective analysis

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Dear Editor, Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma (CTCL). Most patients present with patches and plaques and have an indolent, slowly progressive disease course.[1] In contrast, primary cutaneous γδ T-cell lymphoma (PCGDTCL) is a rare and aggressive CTCL subtype in which tumour cells are characterized by a γδ T-cell receptor (TCR)-δ phenotype and has a rapid clinical progression.[2] A small subset of TCR-δ$^+$ cases with indolent clinical features resembling MF have been reported, raising debate on whether they represent MF or PCGDTCL variants.[3-5] This discussion is complicated by an unknown true prevalence of γδ phenotypes in classical MF (cMF).

To address this gap, regular TCR-δ staining was introduced in our National Cutaneous Lymphoma Centre in August 2023, and we conducted a prospective study of patients with newly diagnosed MF over 1 year. The diagnosis was established through clinicopathological correlation following World Health Organization classification by an expert panel of dermatologists and pathologists confirmed at one of the quarterly meetings of the Dutch Cutaneous Lymphoma Group.[1] To evaluate the TCR phenotype of the tumour cells, immunohistochemical staining for BetaF1 and TCR-δ (clone H-41, Santa Cruz Biotechnology; Dallas, TX, USA) was included in the histopathological workup.

During the 1-year study period, we identified 57 patients with newly diagnosed cMF including six patients (11%) in whom the tumour cells stained positive for TCR-δ. The remaining 51 cases were all positive for BetaF1 and negative for TCR-δ. The median age at diagnosis of the TCR-δ$^+$ cases was 45 (range 15–80) years. Five of these six patients (83%) were diagnosed with early-stage MF (two stage Ia and three stage Ib), one patient had advanced MF (stage IVb) (Table 1). Histopathological and immunophenotypic features were consistent across TCR-δ$^+$ cases. In the five patients with stage Ia/Ib MF the neoplastic cells demonstrated variable epidermotropism and typically expressed CD3 and CD2, with frequent loss of CD5 and CD7 and weak or absent CD4 and CD8 expression. Admixed populations of reactive CD8$^+$ cells served as useful internal controls. Cytotoxic markers TIA-1 and granzyme B were positive in all but one case, explained by the intrinsic cytotoxic function of γδ T cells.[6] In all cases the neoplastic cells stained for TCR-δ and were negative for BetaF1. In the patient with stage IVb MF, large clusters of tumour cells were found in the dermis with large-cell transformation. Immunophenotypic analysis showed that neoplastic cells expressed TCR-δ, CD3, TIA1 and GrB but were negative for CD2, CD5, CD7, CD4 and CD8. Interestingly, partial co-expression of BetaF1 was observed. Dual expression has been described in exceptional cases of CTCL, which might reflect genetic instability.[7] The significance of this co-expression in MF remains unclear and highlights the need for further research into the role of TCR signalling and genomic alterations in disease progression.

The five patients with TCR-δ MF stage Ia/Ib presented with a clinical presentation of early-stage cMF. Following treatment with topical corticosteroids ($n=1$) or phototherapy ($n=4$), patients entered remission ($n=1$) or stable disease ($n=4$), over a median follow-up of 5.5 (range 3–10) months. One patient presented with indurated plaques and ulcerating tumours and demonstrated lymphadenopathy and intramuscular localizations on a positron emission tomography-computed tomography and treatment with systemic chemotherapy was started. Unfortunately, the patient died due to progressive disease within 4 months of diagnosis. This case highlights the challenge of differentiating advanced-stage MF from PCGDTCL, as the aggressive disease course resembles the clinical trajectory typically seen in PCGDTCL. In this particular case, the diagnosis of stage IVb MF was made because the patient had a history of patches and plaques with a prior biopsy revealing epidermotropism consistent with MF.

The observed 11% prevalence of γδ$^+$ MF in this cohort is notably higher than the 2.1% reported by Rodríguez-Pinilla *et al*.[8] This discrepancy may reflect differences in study methodologies, in particular the routine incorporation of γδ TCR staining in conventional diagnostics.

The classification of γδ$^+$ MF remains a subject of debate. Daniels *et al*. have suggested that γδ$^+$ MF cases may share genetic and transcriptional overlaps with PCGDTCL, representing a spectrum of disease.[9] They also acknowledged that the lack of routine γδ TCR testing may introduce selection bias, potentially enriching for aggressive cases. In our prospective cohort, the disease progressed aggressively in only one of six patients, supporting this concern. Larger, unbiased studies with routine TCR profiling are warranted. Despite the limitation of a median follow-up of 5.5 years in this case series, the predominantly indolent clinical presentation observed in our cohort, with the onset of lesions preceding by years the diagnosis in most patients, aligns more closely with cMF, challenging the notion that γδ expression inherently signifies a distinct biological entity. Longer follow-up of these cases is warranted for true insight into the disease course.

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Table 1 Clinical characteristics of six patients with γδ MF

	Characteristics					
Patient no.	1	2	3	4	5	6
Age at onset (years)	15	78	39	49	80	18
Sex	M	F	F	F	F	F
Clinical presentation	Ib (patches and plaques; BSA 40%)	IVb (plaques and tumours; BSA 50%)	Ib (patches; BSA 20%)	Ia (patches; BSA 2%)	Ib (patches; BSA 35%)	Ia (patches; BSA 9%)
Treatment history	Plaquenil, MTX	UVB, radiotherapy	Topical steroids	Topical steroids	Prednisone, topical steroids	Emollients
Time of onset lesions before diagnosis (years)	1	3	7	2	2	8
Immunophenotypic features biopsy	CD2+, CD3+, CD5−, CD7−, CD4−, CD8−, TIA1+, GrB+, TCR-D+, TCR-B−, TOX−, PD1−	CD2−, CD3+, CD5−, CD7−, CD4−, CD8−, TIA1+, GrB+, TCR-D+, TCR-B±, PD1±	CD2+, CD3+, CD5±, CD7−, CD4−, CD8−, TIA1−, GrB−, TCR-D+, TCR-B−, TOX−, PD1−	CD2+, CD3+, CD5±, CD7−, CD4−, CD8−, TIA1+, GrB+, TCR-D+, TCR-B−, TOX+, PD1−	CD2−, CD3+, CD5−, CD7−, CD4−, CD8−, TIA1+, GrB+, TCR-D+, TCR-B−, TOX+, PD1+	CD2+, CD3+, CD5−, CD7−, CD4−,CD8±, TIA1+, GrB+, TCR-D+, TCR-B−, TOX−, PD1−
PET-CT staging performed	Yes: no systemic pathology revealed	Yes: lymphadenopathy and intramuscular localizations	Yes: no systemic pathology revealed	No	No	No
Initial treatment after diagnosis	Topical steroids, UVB	CHOP	Topical steroids, UVB	Topical steroids	Topical steroids, UVB	Topical steroids, UVB
Response	> 50% reduction of lesions	Progressive disease	Stable disease	> 50% reduction of lesions	Stable disease	Stable disease
Follow-up						
Status at last follow-up	AWD	DOD	AWD	AWOD	AWD	AWD
Duration (months)	10	4	6	3	5	7

AWD, alive with disease; AWOD, alive without disease; BSA, body surface area; CHOP, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone; DOD, died of disease; MTX, methotrexate; PET-CT, positron emission tomography–computed tomography; UVB, ultraviolet B

In summary, our findings demonstrate that γδ+ MF may be more common than previously reported, and can be clinically indistinguishable from αβ MF. These observations argue that γδ+ MF should be regarded as a type of MF.

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