Clinical risk factors associated with malignancy in TIF1-γ dermatomyositis

Lydia Cassard BA[1,2], Elizabeth Flatley BA[2,3], Anthony P. Fernandez[2,4] | 1. Cleveland Clinic Lerner College of Medicine; 2. Department of Dermatology, Cleveland Clinic; 3. Rutgers Robert Wood Johnson Medical School; 4. Department of Pathology, Cleveland Clinic

Background

Dermatomyositis (DM) is associated with increased risk of underlying malignancy in patients with autoantibodies to transcriptional intermediary factor 1-γ (TIF1-γ).[1] This risk is highest within 3 years preceding and following DM onset, but many patients may never develop a cancer.[2] Recent findings suggest cancers arising within 1 year of DM present at higher stage and have worse outcomes than cancers arising later. This heterogeneity may be a result of immunoediting with the emergence of cancer reflecting impaired robustness of the immune system.[3] We aimed to characterize a single-center cohort of TIF1-γ(+) DM patients and identify clinical factors associated with malignancy risk.

Methods

We performed a retrospective review of our departmental registry of DM patients. DM diagnosis was confirmed using EULAR/ACR clinical classification criteria. We selected only those with positive autoantibodies to TIF1-γ and with ≥3 years of follow-up data. We compared demographic, clinical, and serologic data in those with malignancy and those without. We compared these variables with respect to the timing of cancer diagnosis relative to DM onset. We additionally assessed the stage and outcome of cancers arising within 1 year of DM and cancers arising later.

Results

Table 1. Characterization of full cohort (n=154)

Female	116 (75.3%)
Age at DM diagnosis*	57 (43, 65)
Classic DM	63 (40.9%)
Amyopathic DM	91 (59.1%)
Cutaneous involvement	
Gottron's papules	131 (85.1%)
Scalp erythema	98 (63.6%)
Poikiloderma	87 (56.5%)
V neck sign	85 (55.2%)
Heliotrope rash	80 (51.9%)
Shawl sign	79 (51.3%)
Periungual erythema	77 (50%)

Our cohort consisted of 154 patients with TIF1-γ(+) DM (**Table 1**). Of these, 116 (75.3%) were female, the median age at DM diagnosis was 57, and 63 (40.9%) had muscle involvement. The most common cutaneous manifestations were Gottron's papules (n=131, 85.1%), scalp erythema (n=98, 63.6%), poikiloderma (n=87, 56.5%), V-neck erythema (n=85, 55.2%), heliotrope rash (n=80, 51.9%), shawl sign (n=79, 51.3%), and periungual erythema (n=77, 50%).

Of the 111 TIF1-γ(+) DM patients for whom ≥ 3 years of follow-up data was available, 26 of these were diagnosed with cancer within 3 years of DM diagnosis and 14 were diagnosed with cancer within 1 year of DM diagnosis (**Table 2**). Factors associated with malignancy diagnosis within 3 years of DM included age > 65 years (p=0.0046), male sex (p=0.0019), muscle involvement (p=0.0237) with elevated CK (p=0.0166), NLR > 3.82 (p=0.0019), and heliotrope rash (p=0.0277). In addition to these, dysphagia (p=0.0296) and ANA titer < 1:160 (p=0.0282) were associated with malignancy diagnosis within 1 year of DM diagnosis.

Of patients with < 4 of these risk factors, 9/82 (11.0%) developed cancer within 3 years of DM diagnosis. Of patients with 4 or more of these risk factors, 17/29 (58.6%) developed cancer within 3 years of DM (p<0.0001). The odds of cancer within 3 years of DM double with each additional risk factor (OR 2.12 [95% CI: 1.52, 2.97], p<0.0001).

Table 2.	Cancer ≤ 1 year, N=14	Cancer 1-3 years, N=12	All others, N=85	p value
Age*	65 (53, 69)	66 (48, 72)	54 (41, 63)	**0.0046**
Male	7 (50%)	5 (41.7%)	14 (16.5%)	**0.0019**
Classic DM	10 (71.4%)	7 (58.3%)	35 (41.2%)	**0.0237**
CK*	414 (79, 5084)	244 (106, 885)	110 (75, 218)	**0.0166**
ANA Positive	8 (66.7%)	11 (91.7%)	67 (82.7%)	0.3300
Titer*	120 (0, 560)	640 (320, 1280)	640 (160, 640)	**0.0282**
NLR*	5.9 (4.3, 12.8)	4 (1.7, 6.3)	3.4 (2.4, 4.7)	**0.0019**
Heliotrope rash	11 (78.6%)	8 (66.7%)	42 (49.4%)	**0.0277**
Dysphagia	7 (50%)	2 (16.7%)	20 (23.5%)	**0.0296**

All data presented as n (%) unless otherwise indicated; * indicates data presented as median (Q1, Q3).

Results

Table 3.	Cancer ≤ 1 year, N=14	Cancer 1-5 years, N=15	Cancer after 5 years, N=8	p value
Stage 1	0	4 (26.7%)	2 (25%)	
Stage 2	3 (21.4%)	4 (26.7%)	2 (25%)	
Stage 3	5 (35.7%)	0	0	**0.0335**
Stage 4	5 (35.7%)	4 (26.7%)	0	
Unknown	1 (7.1%)	3 (20%)	4 (50%)	
In remission	1 (7.1%)	4 (26.7%)	8 (100%)	
Dead of Malignancy	10 (71.4%)	3 (20%)	0	
Dead of complication	2 (14.3%)	1 (6.7%)	0	**0.0005**
Stable	1 (7.1%)	6 (40%)	0	

Cancers diagnosed within 1 year of DM were more likely to be advanced stage (p=0.0335) and associated with worse outcomes (p=0.0005) (**Table 3**).

Conclusion

In patients with TIF1-γ(+) DM, male gender, age > 65 years, muscle involvement with elevated CK levels, heliotrope rash, dysphagia, ANA titer < 1:160, and elevated NLR are associated with underlying malignancy risk. Although malignancy screening is reasonable in all TIF1-γ(+) DM patients, it should be strongly considered in patients with 4 or more of these risk factors. Cancers arising within 1 year of DM diagnosis are more likely to be advanced stage and result in death.

References

1. DeWane ME, Waldman R, Lu J. Dermatomyositis: Clinical features and pathogenesis. Journal of the American Academy of Dermatology 2020;82(2):267–81.

2. Qiang JK, Kim WB, Baibergenova A, Alhusayen R. Risk of Malignancy in Dermatomyositis and Polymyositis. J Cutan Med Surg 2017;21(2):131–6.

3. Fiorentino DF, Mecoli CA, Rosen MC, et al. Immune responses to CCAR1 and other dermatomyositis autoantigens are associated with attenuated cancer emergence. J Clin Invest 132(2):e150201.