# Distinctive cutaneous and systemic features associated with antitranscriptional intermediary factor-1γ antibodies in adults with dermatomyositis

David F. Fiorentino, MD, PhD,[a] Karen Kuo, MD,[a] Lorinda Chung, MD, MS,[b,c] Lisa Zaba, MD, PhD,[a] Shufeng Li, MS,[a] and Livia Casciola-Rosen, PhD[d]
*Redwood City and Palo Alto, California; and Baltimore, Maryland*

***Background:*** Antibodies against transcriptional intermediary factor (TIF)-1γ are associated with malignancy in dermatomyositis (DM). Identification of clinical findings associated with anti-TIF-1γ antibodies in DM is a high priority for both patient diagnosis and risk assessment.

***Objective:*** We sought to define the clinical phenotype of patients with anti-TIF-1γ DM.

***Methods:*** Using a novel, sensitive, and specific assay for anti-TIF-1γ antibodies, we retrospectively tested plasma from 134 adult patients with DM and examined associations between anti-TIF-1γ antibodies and particular clinical and laboratory features.

***Results:*** In all, 55 (41%) patients had autoantibodies to TIF-1γ. Anti-TIF-1γ positive patients were less likely to have systemic features including interstitial lung disease, Raynaud phenomenon, and arthritis/arthralgia. Patients with TIF-1γ autoantibodies had more extensive skin involvement, and some patients manifested characteristic findings including palmar hyperkeratotic papules, psoriasis-like lesions and a novel finding of hypopigmented and telangiectatic ("red on white") patches.

***Limitations:*** This was a retrospective study from a single tertiary referral center.

***Conclusion:*** TIF-1γ is the most commonly targeted DM-specific autoantigen in adults in a large US cohort. Although these patients tend to have less systemic involvement, their skin disease is often extensive and characteristic. Recognition of cutaneous findings in anti-TIF-1γ positive patients may allow more accurate and timely diagnosis and effective treatment of patients with DM. (J Am Acad Dermatol 2015;72:449-55.)

***Key words:*** autoantibodies; Cutaneous Dermatomyositis Assessment and Severity Index; dermatomyositis; malignancy; phenotype; transcriptional intermediary factor-1γ.

Dermatomyositis (DM) is a systemic autoimmune disease characterized by inflammation in multiple organ systems, most commonly the skin and muscle. Patients with DM have circulating autoantibodies; for many of these, the antigenic targets have been characterized.[1,2] At least 6 myositis-specific autoantibody targets have been defined in patients with DM.[3] Because patients with DM and the same autoantibody specificity frequently share similar clinical characteristics, it is likely that precise definition of antibody-associated clinical phenotype will facilitate diagnosis and assessment of systemic risk.

One autoantigen in DM that has recently become the focus of significant interest is transcriptional intermediary factor (TIF)-1γ. TIF-1γ (also called

From the Department of Dermatology[a] and Division of Immunology and Rheumatology,[b] Stanford University School of Medicine, Redwood City; Department of Veterans Affairs Palo Alto Health Care System[c]; and Johns Hopkins University School of Medicine, Division of Rheumatology, Baltimore.[d]

Drs Fiorentino and Rosen are supported by National Institutes of Health (NIH) AR062615-01A1. Dr Rosen is supported by NIH RO1 AR-44684 and the Donald and Dorothy Stabler Foundation. The Johns Hopkins Rheumatic Diseases Research Core Center, where the assays were performed, is supported by NIH P30-AR-053503.
Conflicts of interest: None declared.

Accepted for publication December 8, 2014.

Reprint requests: David F. Fiorentino, MD, PhD, Department of Dermatology, Stanford University School of Medicine, 450 Broadway, C-234, Redwood City, CA 94063. E-mail: fiorentino@stanford.edu.

Published online January 14, 2015.
0190-9622/$36.00



http://dx.doi.org/10.1016/j.jaad.2014.12.009

TRIM33, p155/140) belongs to the larger tripartite motif (TRIM) family of proteins that are implicated in a number of important biological processes, including cell proliferation, development, apoptosis, and innate immunity. Anti-TIF-1γ antibodies have been reported in 13% to 21% of adults with DM.[4] Several studies have now shown that patients with DM and anti-TIF-1γ antibodies are at higher risk of internal malignancy.[4-6] In addition, several studies suggest that these patients are at relatively low risk of interstitial lung disease (ILD).[4,5,7-9] However, there are few studies describing the cutaneous manifestations of this antibody subgroup in adults with DM, and the data are conflicting regarding relative frequencies of skin findings.[4,5,8,10] Providing additional information regarding this phenotype may aid in understanding disease pathogenesis and help clinicians identify these anti-TIF-1γ positive patients at the bedside.

**CAPSULE SUMMARY**

- Transcriptional intermediary factor-1γ is an autoantigen targeted in patients with dermatomyositis.
- Patients with dermatomyositis and transcriptional intermediary factor-1γ autoantibodies have more extensive skin disease and can have characteristic cutaneous findings including palmar hyperkeratotic papules, psoriasis-like lesions, and hypopigmented and telangiectatic patches.
- Careful skin examination can help identify patients with dermatomyositis and antitranscriptional intermediary factor-1γ antibodies.

## METHODS

### Patients

Patients with DM (age >18 years) were seen in the outpatient clinics at the Stanford University Department of Dermatology between July 2004 and April 2013. Patients were followed up for multiple visits (on average every 3-6 months) with a median time of follow-up of 361 days. The Stanford Institutional Review Board approved the collection of plasma and clinical information. Patients were considered to have DM if they met "probable" or "definite" criteria for DM based on Bohan and Peter[11,12] criteria or, for clinically amyopathic patients, if they fulfilled the proposed cutaneous criteria of Euwer and Sontheimer.[13] Patients were considered clinically amyopathic if they had cutaneous disease for at least 6 months and had no evidence of muscle weakness and no elevation of muscle enzymes. Skin disease was recorded biannually using the Cutaneous DM Assessment and Severity Index (CDASI).[14,15] Unless otherwise noted, each clinical feature was dichotomized as present or absent, the former based on if the patient *ever* displayed that feature during the course of follow-up. All systemic symptoms were retrospectively reviewed from charts. ILD was defined as the presence of ground-glass opacities and/or fibrotic changes on high-resolution computed tomography scanning of the chest. Patients were considered to have cancer-associated DM if their first sign or symptom of cancer was within 3 years of their first DM symptom. All patients received a chest/abdomen/pelvic computed tomography scan at least once within the first 3 years of their disease for malignancy screening.

### Antibody detection

Plasma was collected at the time of their first visit, and many patients were already on topical and/or systemic immunosuppressive therapy at the time of plasma collection. Antibodies against TIF-1γ, Mi-2, nuclear matrix protein 2 (NXP2), small ubiquitin-like modifier (SUMO-1) activating enzyme 1, Jo-1, and melanoma differentiation-associated gene 5 (MDA5) were determined as previously described.[16]

### Statistics

Wilcoxon rank sum test was used to compare continuous variables and 2-sided Fisher exact test was used to compare categorical variables. *P* values less than .05 were considered statistically significant. Analyses were conducted using SAS (Version 9.3, SAS Institute Inc, Cary, NC).

## RESULTS

### Patient characteristics and autoantibody frequencies

Major demographic and systemic features of the cohort are shown in Table I. The cohort was mostly (72%) female with a median age of 48.4 years (range 4.6-86.9 years) at age of diagnosis and had an average of 5.3 ± 5.1 years of follow-up. A total of 28 (21%) patients were clinically amyopathic, 22 (16%) had ILD, and 28 (21%) had a cancer-associated DM.

Of 134 patients, 111 (83%) had at least 1 circulating autoantibody against 1 of the tested antigens. Plasma from 12 (9%) patients reacted with 2 or more antigens, with the specific combinations and frequencies (in parentheses) as follows: TIF-1γ and Mi-2 (7); TIF-1γ and Jo-1 (1); TIF-1γ, Mi-2, and NXP2