Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

TIF1-γ Positive Dermatomyositis with Spontaneous Muscular Hematoma in the Context of Ovarian Cancer: A Novel Survival Case Report

Zhu Yuan[1,*], Chunyan Chen[1,*], Shuai Zeng[2], Zhen Wang[1], Shili Zhong[1]

[1]Department of Intensive Care Medicine, Army Medical Center of PLA, Chongqing, People's Republic of China; [2]Department of Laboratory Pathology, Unit 32280 of the People's Liberation Army, Leshan City, Sichuan Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shili Zhong, Department of Intensive Care Medicine, Army Medical Center of PLA, No. 10 Changjiang Road, Yuzhong District, Chongqing, 400010, People's Republic of China, Tel +86-18323087674, Email 805646578@qq.com

Background: Dermatomyositis (DM) represents a group of inflammatory myopathies, with TIF1-γ positive DM strongly associated with malignancies. Spontaneous muscular hematoma in DM patients is exceedingly rare and often prognosticates a severe clinical outcome, especially in the context of concurrent malignancy.

Case Presentation: We describe a novel survival case of a patient with TIF1-γ positive DM and an underlying ovarian tumor who developed a spontaneous muscular hematoma. Despite the traditionally poor prognosis of these conditions, the patient survived through a comprehensive treatment regimen. This included targeted chemotherapy for ovarian cancer (Carboplatin and Paclitaxel), alongside corticosteroids, immunoglobulins, and immunosuppressants for DM, as well as component blood transfusions, coagulation correction therapy to control hematoma, and integrated management: nutritional support, lung function exercise, volume management.

Results: The integrated treatment strategy stabilized the patient's condition and resolved the hematoma, a significant achievement given the usual high mortality rate of such complications.

Conclusion: This case underscores the importance of a multidisciplinary approach in the early diagnosis and treatment of TIF1-γ positive DM with complex comorbidities, including spontaneous muscular hematoma and ovarian cancer. It highlights the potential for favorable outcomes with aggressive and coordinated treatment strategies.

Keywords: dermatomyositis, TIF1-γ, spontaneous muscular hematoma, ovarian cancer, multidisciplinary treatment, survival

Introduction

Dermatomyositis (DM) is an autoimmune disorder with systemic involvement characterized by distinctive cutaneous manifestations, including heliotrope rash, Gottron's papules, and nail fold changes, alongside symmetrical proximal muscle weakness, which may lead to complications like dysphagia and respiratory issues.[1] The development of severe complications, notably interstitial lung disease and spontaneous muscle hemorrhage, substantially diminishes the prognosis for DM patients.[2,3]

Research has identified various myositis-specific antibodies (MSAs) in DM, each associated with unique clinical phenotypes and prognoses, such as anti-MDA5, anti-TIF1-γ, anti-Mi-2, anti-NXP2, and anti-Jo-1.[4,5] While MSAs typically do not overlap, multiple antibodies can complicate clinical presentation and treatment.[6]

TIF1-γ positive DM, categorized as cancer-associated myositis (CAM), demonstrates a significant correlation with malignancies, marking it as a critical risk factor for cancer.[7] Meanwhile, dermatomyositis combined with spontaneous muscle hematoma has a high mortality.[3] This manuscript delves into a rare case of severe spontaneous intramuscular hematoma in a patient with TIF1-γ positive DM against the backdrop of an ovarian tumor, highlighting the intricate interplay between DM and its life-threatening complications.

Received: 21 March 2024
Accepted: 12 June 2024
Published: 18 June 2024

Case Presentation

Initial Presentation

A 50-year-old woman presented to the oncology department with abdominal distension and ascites. Diagnostic efforts, including ascites puncture, cytology, and whole-body PET/MRI, confirmed Stage IVB bilateral ovarian high-grade serous carcinoma (Figure 1).

Diagnosis and Initial Treatment

Initial chemotherapy with carboplatin and albumin-bound paclitaxel was administered. Concurrent dermatological symptoms prompted a consultation, suggesting dermatomyositis, which was treated with methylprednisolone and diuresis. Despite anticoagulation therapy with low molecular weight heparin due to a hypercoagulable state, the patient's condition is complicated with significant facial edema, dysphagia, and decreased muscle strength, leading to a multidisciplinary team (MDT) review.

Advanced Management

The MDT's suspicion of dermatomyositis led to specific antibody screening and intensified treatment with higher doses of methylprednisolone, immunoglobulin pulse therapy, and cyclophosphamide. Despite these efforts, the patient developed severe anemia and spontaneous muscle hemorrhage (Figure 2), necessitating emergency interventions and ICU admission for high-flow respiratory support and further treatment adjustments.

Complications & Final Management

Complications included a drastic hemoglobin drop and suspected active bleeding, managed with transfusions and intensive care. The patient's condition stabilized, allowing for the continuation of oncologic and rheumatologic care, with ongoing vigilance for interstitial lung disease and thromboembolic risks.

Discussion

Dermatomyositis with spontaneous muscle hematoma represents an exceptionally rare complication in dermatomyositis patients. Notably, the incidence of cancer in patients with TIF1-γ-positive dermatomyositis aged 39 years and older is significantly elevated compared to their younger counterpart.[8] Moreover, the progression of malignancy has been positively associated with the titer of TIF1-γ.[9] Literature review indicates that spontaneous intramuscular hemorrhage in

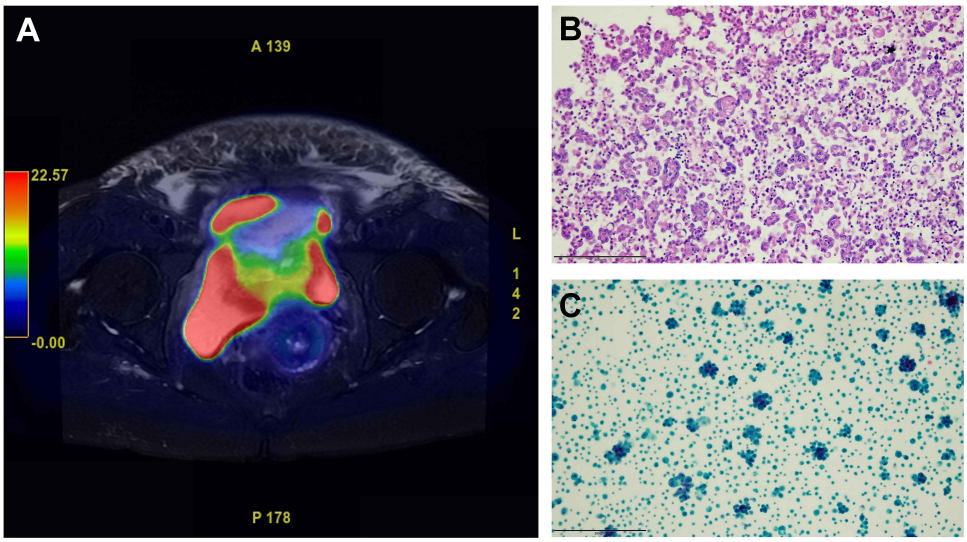

Figure 1 (**A**) PET/CT: FAPI-PET shows increased radioactive uptake in bilateral ovarian adnexal regions. (**B** and **C**) Pathology and immunohistochemistry show high-grade serous tumor cells in the ovary. The size bar for subfigures (**B** and **C**) 200μm.

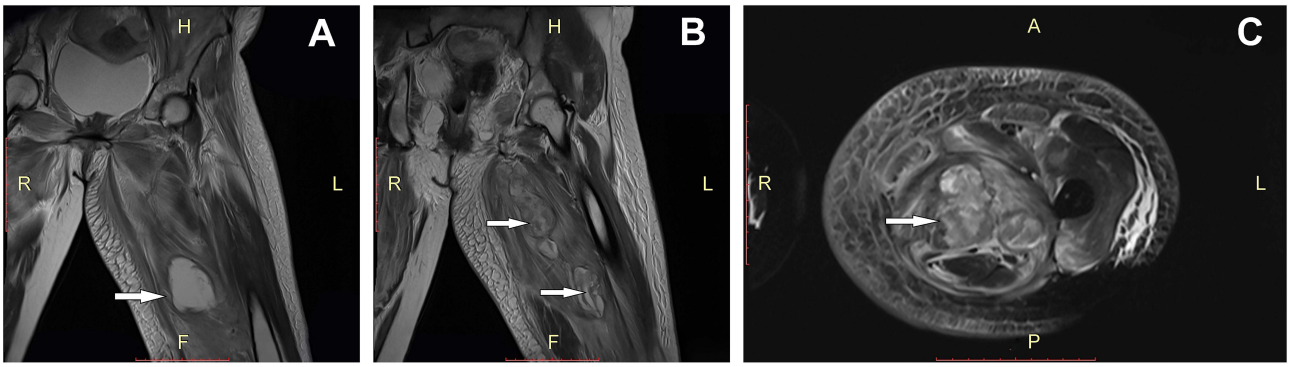

Figure 2 Magnetic resonance imaging of the patient's left lower limb (**A-C**). The arrow marks the location of the hematoma. Hematoma volume: (**A**) (62.2mm×42.7mm), (**B**) (96.2mm×27.7mm;51.8mm×24.0mm), (**C**) (49.3mm×32.0mm).

dermatomyositis is predominantly observed in patients with anti-MDA5-positive dermatomyositis, followed by those positive for anti-Ro52.[10] Furthermore, the overall mortality rate for dermatomyositis patients experiencing spontaneous muscle hemorrhage stands alarmingly high at 60.9%.[3,10] In the context of this case, a 50-year-old patient with an underlying ovarian tumor was diagnosed with TIF1-γ-positive dermatomyositis, subsequently developing rare muscle hemorrhage. The patient survived following conservative management, including blood transfusion. In the shared case by LiFraine, S., ovarian cancer was diagnosed alongside dermatomyositis, with spontaneous hemorrhage of the iliopsoas muscle manifesting post-IVIG infusion. Coupled with a positive Coombs test, the patient was identified to have autoimmune hemolysis, complicating the bleeding etiology.[11] Interestingly, in our case, bleeding in the left lower limb emerged on the third day post-IVIG pulse therapy, yet hemolysis was excluded following comprehensive bilirubin and hemolysis assessments. Although IVIG-associated hemolysis reports are scarce and typically self-limiting,[12] vigilance for IVIG-mediated immune hemolysis is crucial in dermatomyositis with bleeding risk to prevent disease progression delay. Endothelial cells, fundamental to blood vessel formation and repair, play a pivotal role, and their dysfunction in dermatomyositis may contribute to adverse vascular outcomes, including severe spontaneous muscle hemorrhage, as suggested by increased vascular injury markers and hindered endothelial progenitor cell regeneration in these patient.[13,14] This posits endothelial dysfunction induced by dermatomyositis as a potential mechanism warranting further investigation.

Due to the patient's severe anemia and compromised oxygenation, a transfer to the intensive care unit was deemed necessary, with a provisional diagnosis of dermatomyositis potentially complicated by interstitial pneumonia. In this case, the presence of TIF1-γ, anti-PM-Scl75, and anti-Ro-52 antibodies was noted, mirroring the findings of Brown, Z.R, where the patient exhibited positivity for anti-Ro52 and anti-NXP-2 antibodies alongside a spontaneous lower limb hematoma, ultimately benefiting from five cycles of plasmapheresis.[15] The presence of anti-Ro-52 antibodies in dermatomyositis is recognized as an independent risk factor for the development of interstitial lung disease (ILD), whereas positivity for anti-TIF1-γ antibodies is traditionally viewed as a protective factor against ILD complications in dermatomyositis patients.[16] However, Zhang, H. reported an intriguing case of rapid progression to ILD mediated by pneumocystis pneumonia in a dermatomyositis patient positive for anti-TIF1-γ antibodies. The rarity of ILD in patients with anti-TIF1-γ-positive dermatomyositis may be attributable to the swift initiation of immunosuppressive therapy and underlying nutritional deficiencies.[17] The co-expression of TIF1-γ and Ro-52 antibodies in our patient raised concerns for the potential development of interstitial pneumonia. Nonetheless, over a month since the onset, subsequent chest CT scans have not revealed any indications of pulmonary interstitial pneumonia, suggesting a complex interplay of immunological factors in the manifestation and progression of interstitial lung disease in dermatomyositis.

During the course of diagnosing dermatomyositis, our patient developed severe facial edema, leading to dysphagia, followed by subcutaneous edema in the left lower extremity. This presentation bears resemblance to cases reported by Nishioka, H., among others.[18] However, the edema in our patient was notably localized to the face and left lower limb, contrasting with the widespread generalized edema observed in some cases. The occurrence of severe subcutaneous edema in patients positive for TIF1-γ antibodies with dermatomyositis suggests a potential underlying mechanism that has yet to be elucidated. We plan to continue monitoring the evolution of the facial and lower limb edema in this case

closely. Given the severity of systemic edema, particularly when involving the larynx, it is advisable to perform a laryngoscopic examination to assess the need for tracheotomy promptly. For our patient, who exhibited severe facial edema, timely laryngoscopic examination was conducted, effectively ruling out laryngeal edema. This proactive approach underscores the importance of thorough assessment and intervention in managing dermatomyositis complications, ensuring prompt identification and management of potentially life-threatening conditions.

The pathogenesis of dermatomyositis remains elusive, yet the up-regulation of interferon (IFN) signaling is strongly associated with the disease's progression in affected individuals.[19] Current therapeutic strategies, primarily comprising steroids and intravenous immunoglobulins (IVIG), target symptoms rather than the disease's root causes. Janus kinase (JAK) inhibitors, including baricitinib, upadacitinib, and tofacitinib, have emerged as promising treatments. These medications block IFN signal transduction and suppress the expression of inflammation and regeneration-associated genes, thereby ameliorating patient symptoms.[20]

Recent advancements in understanding dermatomyositis have been propelled by transcriptome and proteomic analyses. A study by Ward, J.M., involving 14 adult and 12 adolescent patients with dermatomyositis, identified that beyond the IFN signaling pathway, the PI3K/AKT, ERK, and p38 MAPK signaling pathways are commonly enriched among sufferers. Additionally, upstream components such as membrane receptors TLR2, TLR4, HAVCR2, EPOR, CSF2RA, and FGFR were found to be significantly up-regulated.[21] This discovery opens new avenues for the diagnosis and therapeutic intervention in dermatomyositis, suggesting a myriad of potential targets that extend beyond the traditionally focused IFN pathway. However, translating these insights into practical treatments necessitates further foundational and clinical research. The identification of these signaling pathways and receptor up-regulations not only deepens our understanding of dermatomyositis pathophysiology but also underscores the complexity of its underlying mechanisms. As the scientific community continues to unravel these intricate pathways, the potential for developing targeted therapies that address the core pathogenic processes of dermatomyositis becomes increasingly tangible.

In this case, the diagnosis of TIF1-γ positive dermatomyositis was carefully considered and ultimately confirmed following the identification of skin lesions and severe facial edema, subsequent to a clear cancer diagnosis. Distinguishing dermatomyositis from tumorigenesis poses challenges, yet the association between dermatomyositis and malignancy is undeniable. Studies, including those by Yang, H., have reiterated that TIF1-γ positive dermatomyositis is a form of cancer-associated myositis, with fluctuations in TIF1-γ antibody levels serving as potential predictors for tumor progression or patient prognosis.[22] Conversely, research conducted by Fiorentino, D.F.et al, revealed the presence of additional autoantibodies, such as anti-CCAR1 antibodies, in patients with TIF1-γ positive dermatomyositis who do not have cancer. This finding suggests a negative correlation with tumor occurrence and progression.[23] Furthermore, Aussy, A., and colleagues have identified that TIF1-γ antibody-positive patients with IgG2 positivity are significantly associated with cancer risk, positing anti-TIF1-γ IgG2 as a novel cancer marker useful in assessing mortality risk in patients with TIF1-γ positive dermatomyositis.[24] In light of these findings, we advocate for the early screening of TIF1-γ antibodies in patients where dermatomyositis is suspected. Such proactive measures could potentially alter the trajectory of adverse events in these patients at an early stage, underscoring the importance of integrating immunological markers in the diagnostic and prognostic assessment of dermatomyositis, particularly in the context of its association with malignancies.

Fortunately, in this case, the patient experienced improvement in spontaneous bleeding following conservative management with blood transfusion. This outcome is particularly noteworthy given that in previous reports, the mortality rate for patients with deep muscle hemorrhages, such as those affecting the iliopsoas muscle, reached up to 80%, in contrast to a 25% fatality rate for those with superficial muscle hematomas.[12] The accurate localization of the bleeding site, along with early screening for coagulation disorders and thrombosis, supported by bedside ultrasound, MRI, and other diagnostic tools, proved essential. Drawing from our experience, we recommend a balanced transfusion strategy involving suspended red blood cells, fresh frozen plasma, and cryoprecipitate in a 1:1:1 ratio. Moreover, the coagulation process and the formation of blood clots rely on fibrinogen, underscoring the importance of timely fibrinogen supplementation for effective hemostasis. Regular monitoring and reassessment through complete blood counts, coagulation profiles, and thromboelastography are indispensable components of patient management. There are still limitations in our early diagnosis. We did not timely consider the diagnosis of dermatomyositis when the patient had initial facial edema.

Because the patient's ovarian cancer was clearly diagnosed, it was considered that the possibility of paraneoplastic syndrome was high.

Conclusion

The presence of a malignant tumor disrupts the coagulation system, with routine anticoagulation outlined in clinical guidelines. However, when dermatomyositis is present, anticoagulation therapy requires careful consideration due to potential contradictions. Long-term endothelial damage, capillary wall fragility, and the administration of steroids in dermatomyositis patients may predispose to vascular rupture and subsequent bleeding. Therefore, in patients with concurrent tumors and dermatomyositis, prophylactic anticoagulation and steroid use should be approached with caution. Comprehensive coagulation assessments, including thromboelastography, early thrombosis screening (TAT/t-PAIC), and measurement of the plasmin-α2 plasmin inhibitor complex, are recommended when necessary. For patients with dermatomyositis and a tumor background, monitoring specific antibody levels, such as TIF1-γ, is beneficial for evaluating patient prognosis and guiding therapeutic decisions.

Ethical Approval and Consent to Participate

The study was approved by the Ethics Committee of Hospital of Army Medical Center of PLA. Written informed consent was obtained from the patient for the publication of all the images and data included in this article. Ethical review and approval were not required to publish the case details in accordance with the institutional requirements.

Consent to Publish

The patient has consented to the submission of the case report to the journal.

Acknowledgments

We are immensely grateful to our generous patients for allowing us to publish their cases.

Author Contributions

Zhu Yuan is the first author, Chunyan Chen is the co-first author, and Shili Zhong is the only corresponding author, All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Chongqing Medical Key Discipline Development Project (No.2dxk202102).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Tanboon J, Nishino I. Update on dermatomyositis. *Curr Opinion Neurol*. 2022;35(5):611–621. doi:10.1097/WCO.0000000000001091
2. Wu W, Guo L, Fu Y, et al. Interstitial Lung Disease in Anti-MDA5 Positive Dermatomyositis. *Clinical Reviews in Allergy & Immunology*. 2021;60(2):293–304. doi:10.1007/s12016-020-08822-5
3. Xing R, Xiang F, Dong L, et al. Spontaneous intramuscular hemorrhage in cancer-associated dermatomyositis: a case and literature review. *BMC Musculoskeletal Disorders*. 2023;24(1):542. doi:10.1186/s12891-023-06651-z
4. Cobos GA, Femia A, Vleugels RA. Dermatomyositis: an Update on Diagnosis and Treatment. *Am j Clin Dermatol*. 2020;21(3):339–353. doi:10.1007/s40257-020-00502-6
5. Mammen AL. Dermatomyositis and polymyositis: clinical presentation, autoantibodies, and pathogenesis. *Ann. N.Y. Acad. Sci.* 2010;1184(1):134–153. doi:10.1111/j.1749-6632.2009.05119.x

6. Muro Y, Ishikawa A, Sugiura K, Akiyama M. Clinical features of anti-TIF1-α antibody-positive dermatomyositis patients are closely associated with coexistent dermatomyositis-specific autoantibodies and anti-TIF1-γ or anti-Mi-2 autoantibodies. *Rheumatology*. 2012;51(8):1508–1513. doi:10.1093/rheumatology/kes073
7. Wong VT, So H, Lam TT, Yip RM. Myositis-specific autoantibodies and their clinical associations in idiopathic inflammatory myopathies. *Acta Neurol Scand*. 2021;143(2):131–139. doi:10.1111/ane.13331
8. Oldroyd A, Sergeant JC, New P, et al. The temporal relationship between cancer and adult onset anti-transcriptional intermediary factor 1 antibody-positive dermatomyositis. *Rheumatology*. 2019;58(4):650–655. doi:10.1093/rheumatology/key357
9. Yang H, Yan T, Zhang X, et al. Clinical significance of anti-transcriptional intermediary factor 1-γ antibody in patients with dermatomyositis: a monocentric cross-sectional study. *Clin Rheumatol*. 2022;41(8):2439–2448. doi:10.1007/s10067-022-06170-7
10. Xu Z, Lv X, Xu W, et al. Spontaneous Intramuscular Hemorrhage in Anti-MDA5 Positive Dermatomyositis: a Case Series and Literature Review. *Front Med*. 2021;8:802753.
11. Li Fraine S, Coman D, Vallée Guignard V, Costa JP. Spontaneous Retroperitoneal Hemorrhage in Dermatomyositis. *Am j Med*. 2021;134(2):e137–e138. doi:10.1016/j.amjmed.2020.06.038
12. Mohamed M, Bates G, Eastley B. Massive intravascular haemolysis after high dose intravenous immunoglobulin therapy. *Br. J. Haematol.* 2013;160(5):570. doi:10.1111/bjh.12182
13. Kishi T, Chipman J, Evereklian M, et al. Endothelial Activation Markers as Disease Activity and Damage Measures in Juvenile Dermatomyositis. *J Rheumatol*. 2020;47(7):1011–1018. doi:10.3899/jrheum.181275
14. Lemmer D, Schmidt J, Kummer K, et al. Impairment of muscular endothelial cell regeneration in dermatomyositis. *Front Neurol*. 2022;13:952699. doi:10.3389/fneur.2022.952699
15. Brown ZR, Thomas JS, Limaye V. A case of haemorrhagic myositis with concurrent anti-Ro52 and anti-NXP-2 antibodies treated with plasmapheresis. *Rheumatology*. 2020;59(3):682–684. doi:10.1093/rheumatology/kez365
16. Xing X, Li A, Li C. Anti-Ro52 antibody is an independent risk factor for interstitial lung disease in dermatomyositis. *Respir Med*. 2020;172:106134. doi:10.1016/j.rmed.2020.106134
17. Zhang H, Yue J, Hou X, et al. Rapidly progressive interstitial lung disease combined with pneumocystis jiroveci pneumonia in a patient with single anti-TIF-1γ antibody positive dermatomyositis in the context of an underlying tumor. *BMC Pulm Med*. 2023;23(1):248. doi:10.1186/s12890-023-02542-0
18. Nishioka H, Shindo T, Shimizu H. Dermatomyositis Presenting with Generalized Subcutaneous Edema. *Internal Med*. 2023;62(15):2273–2277. doi:10.2169/internalmedicine.0687-22
19. Tabata MM, Hodgkinson LM, Wu TT, et al. The Type I Interferon Signature Reflects Multiple Phenotypic and Activity Measures in Dermatomyositis. *Arthritis Rheumatol*. 2023;75(10):1842–1849. doi:10.1002/art.42526
20. Paik JJ, Lubin G, Gromatzky A, Mudd PN, Ponda MP, Christopher-Stine L. Use of Janus kinase inhibitors in dermatomyositis: a systematic literature review. *Clin exp rheumatol*. 2023;41(2):348–358. doi:10.55563/clinexprheumatol/hxin6o
21. Ward JM, Ambatipudi M, O'Hanlon TP, et al. Shared and Distinctive Transcriptomic and Proteomic Pathways in Adult and Juvenile Dermatomyositis. *Arthritis Rheumatol*. 2023;75(11):2014–2026. doi:10.1002/art.42615
22. Dani L, Holmqvist M, Martínez MA, et al. Anti-transcriptional intermediary factor 1 gamma antibodies in cancer-associated myositis: a longitudinal study. *Clin exp rheumatol*. 2020;38(1):67–73.
23. 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*. 2022;132(2). doi:10.1172/JCI150201
24. Aussy A, Fréret M, Gallay L, et al. The IgG2 Isotype of Anti-Transcription Intermediary Factor 1γ Autoantibodies Is a Biomarker of Cancer and Mortality in Adult Dermatomyositis. *Arthritis Rheumatol*. 2019;71(8):1360–1370. doi:10.1002/art.40895