CLINICAL CHARACTERISTICS OF ADULT DERMATOMYOSITIS PATIENTS WITH ANTI-TRANSCRIPTION INTERMEDIARY FACTOR 1-GAMMA POSITIVE

BY

AMADEU ROMALDO XIMENES AMARAL MENDES

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE
IN DERMATOLOGY AND DERMATOSURGERY
(INTERNATIONAL PROGRAM)
COLLEGE OF MEDICINE

GRADUATE SCHOOL, RANGSIT UNIVERSITY
ACADEMIC YEAR 2024

Thesis entitled

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was submitted in partial fulfillment of the requirements
for the degree of Master of Science in Dermatology and Dermatosurgery
(International Program)

Rangsit University
Academic Year 2024

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May 9, 2025

ACKNOWLEDGEMENTS

I am profoundly grateful to my advisor, Pinnaree Katipattanapong, M.D. For her exceptional guidance, unwavering support, and mentorship throughout my academic journey. Her expertise, encouragement, and dedication have been instrumental in shaping the success of this research endeavor.

I extend my heartfelt thanks to the Institute of Dermatology, for providing a conducive environment, resources, and opportunities for research. The institute's commitment to excellence and innovation has been pivotal in the development and execution of this study.

I also wish to acknowledge the TICA Scholarship for their generous financial support, which has enabled me to pursue my academic aspirations and contribute to the field of Dermatology. Their assistance has played a significant role in facilitating my education and research endeavors.

The combined support and collaboration of my advisor, the Institute of Dermatology, and the TICA Scholarship have been invaluable in realizing this project. Their contributions have been indispensable, and I am deeply appreciative of their involvement in this academic endeavor.

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6509838	:	Amadeu Romaldo Ximenes Amaral Mendes
Thesis Title	:	Clinical Characteristics of Adult Dermatomyositis Patients with anti-Transcription Intermediary Factor 1-Gamma Positive
Program	:	Master of Science in Dermatology and Dermatosurgery (International Program)
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Abstract

Dermatomyositis, an idiopathic inflammatory myopathy, presents with varied clinical manifestations and immune profiles, posing diagnostic and therapeutic challenges. This systematic review examined 11 cohort studies involving 261 adult dermatomyositis (DM) patients with anti-TIF1 γ antibodies. Predominantly female 76.6% with a median onset age of 54.2 years, patients were mostly from Asian ethnicities 77.4%. Median follow-up was 48 months, with a median time from DM diagnosis to cancer development of 4.75 months. The median age at cancer diagnosis was 61.75 years, with a median time from diagnosis to death of 8.3 months. Malignancy was associated with 45.4% of patients.

Common cutaneous manifestations included heliotrope rash 78.0% and Gottron's sign 58.1%. Musculoskeletal symptoms comprised proximal muscle weakness at 81.6% and myalgia at 36.2%. Pulmonary involvement occurred in 12.3% of patients. The most frequent malignancies seen in cases of dermatomyositis with anti-TIF1 gamma antibodies include nasopharyngeal 11.8%, lung 11.0%, and breast 10.1% cancers from 119 cases. The mortality rate associated with this condition is noted to be 11.2%. Further research is needed to elucidate underlying pathogenic mechanisms and optimize patient management.

(Total 51 pages)

Keywords: Adult Dermatomyositis, Anti-Transcription Intermediary Factor 1 Gamma Positive, Clinical Characteristics

Student's Signature …..... Thesis Advisor's Signature .....

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CHAPTER 1

INTRODUCTION

1.1 Background and Significance of the Problem

Idiopathic inflammatory myopathies (IIM) are a diverse collection of inherited muscle illnesses and unknown causes. The various entities are linked with a wide range of clinical symptoms, including involvement of inflammatory muscles, from amyopathic to necrotic, and the usual involvement of internal organs and skin. Based on the clinical manifestation, histopathological and serological data are particularly helpful for disease classification and stratification. (Mantegazza, Bernasconi, Confalonieri, & Cornelio, 1997). IIM may be categorized into many primary sub-types and dermatomyositis (DM), is one of them. (Preuße et al., 2012; Nagaraju et al., 2005). Two classes of antibodies have been postulated within the antibody spectrum. (Eisa-Beygi, Hatch, Noble, Ekker, & Moon, 2013), Myositis-specific antibodies (MSAs) are named after their unique relationship with IIM, whereas myositis-associated antibodies (MAAs) are named by their occurrence in several connective tissue diseases. Based on the findings of this work, a new researcher can focus more specifically on clinical features, pathogenesis, and early care of this subs-specific myositis antibody in order to prevent unfavorable prognosis in the future.

Similar to numerous additional autoimmune systemic illnesses, it is uncertain whether or not the reported autoantibody production is actually related to disease pathogenesis or merely an epiphenomenon. Nevertheless, the strong link between particular autoantibodies and a unique clinical phenomenology, as well as their high disease specificity and use for illness classification and prognosis, indicates that they might contribute to the development and spread of disease. (Gunawardena, Betteridge,

& McHugh, 2009). The table below covers in detail the nature and function of the anti-TIF1 gamma-specific antigens that have so far been found. A comprehensive list of antigens and autoantibodies found in adult and pediatric patients with anti-TIF1 γ is provided below.

The table 1.1 below describes Myositis-Specific Antigens (MSAs) that are being studied. Focus on Dermatomyositis (DM) with anti-TIF 1 **γ.**

Table 1.1 Incidence, Detection Methods, and Molecular Characteristics of TIF-1 γ in Juvenile and Adult Malignancy-Associated Myositis

Autoantigen and function	Molecular Weight	Cellular Localization	Illness and its Manifestations	Incidence in juvenile (J) and adult (A) IIM	Commercial and Traditional Detecting Systems	References
TIF-1γ E3-Ligase, transcriptional factor-1γ hetero complex	155/140 kDa	Nu	Malignancy associated DM in adults, however skin ulcer in juvenile DM	(A)13-21% (J)22–29%	IF[1], WB[2], IIFT[3], Strip test	(Targoff et al., 2006. And Gunawardena H. et al., 2008).

Remark [1]Immunofluorescence, Indirect Immunofluorescence[2], Western Blot[3]

Source: Stuhlmüller, 2019

TIF-1 (transcription intermediary factor-1 gamma) is the particular antigen. This multifunctional protein with a MW of 155/140 (kDa) is primarily engaged in gene transcription. (Fiorentino et al., 2012). Cell growth, proliferation, apoptosis, and innate immunity are all impacted by TIF-1 proteins, which are tripartite motif-containing (TRIM) proteins. (Kawai & Akira, 2011). A plant homeodomain finger and a bromo-domain (BROMO), which is highly conserved among TIF1 family members but absent from other TRIM proteins, make up the C-terminal chromatin reading unit shared by all TIF1 proteins. (Khetchoumian et al., 2004). While TIF1 is the most prevalent target in anti-TIF1-positive CAM (cancer-associated myositis), additional

TIF1 family proteins may also be concurrently targeted by the immune system (Fujimoto et al., 2012).

A feature known as the tripartite-containing motif (TRIM), these proteins can also act as E3-ligases in the ubiquitination: The E1, E2, and E3 pathways regulate the function, location, and degradation of proteins. In this regard, it is worth noting that TIF1- is implicated in the control of TGF- signaling by mono-ubiquitination of SMAD-4, which leads to TGF- inhibition. TIF1- might thus have a critical function in promoting or preventing cancer cell growth and differentiation by boosting cell proliferation and differentiation. (Agricola, Randall, Gaarenstroom, Dupont, & Hill, 2011). The established relationship of anti-TIF1- antibodies with an increased risk of malignant development in DM shows that this link may not be coincidental. Anti-TIF antibodies were infrequently detected in individuals with solid tumors (3.1%) or rheumatic paraneoplastic illness (3.3%) who did not have DM. (Venalis, Selickaja, Lundberg, Rugiene, & Lundberg., 2018).

Mutations and loss of heterozygosity (LOH) in TIF1 genes are among the many genetic abnormalities seen in tumors from anti-TIF1-positive paraneoplastic patients, according to current research. (Pinal-Fernandez et al., 2018.) Additionally, compared to type-matched control tumors from patients without myositis, TIF1-staining was significantly stronger in the tumors and muscle tissue of anti-TIF1-positive individuals. This information may suggest that tumors with high levels of TIF1 protein manifestation and mutations in TIF1 peptide regions with high affinity for HLA class I may co-occur and cause a strong adaptive immune response against the mutant cancerous cells. It's interesting to note that LOH is the most frequent way for a mutant allele to be lost in human malignancy. This is significant for tumor immune-editing because the immune system may remove tumor cells with antigenic mutations and replace them with tumor cells that have LOH in that area (without the antigenic mutation). (Joseph et al., 2014). As a result, these changes can elicit an immune response while also allowing the tumor cell to evade clearance.

It has been shown that DM illness progresses toward the equator and is highly related to latitude. Another research recently validated this finding that the relative incidence of DM and the frequency of anti-TIF1- autoantibodies were substantially inversely linked with latitude in adults with myositis. Furthermore, the HLA alleles HLA-DRB1* 07:01 and HLA-DQB1*02 were substantially linked to the DM-specific autoantibodies anti-Mi-2 and anti-TIF1. (Parkes, Rothwell, Oldroyd, Chinoy, & Lamb, 2018).

Anti-TIF1 (anti-155/140) antibodies are found in 13-21% of patients with tumor-associated adult DM and roughly 30% of individuals with severe juvenile DM (Gunawardena et al., 2008). These antibodies are the most common marker in juvenile IIM (JIIM) and are strongly linked to JDM. Initially, they were detected nearly exclusively in JDM, in around 23-29% of patients utilizing immunoprecipitation and immunoblotting. Adult cancer has been associated with TIF-antibodies with 89% specificity, 78% sensitivity, and 58 and 95% positive and negative predictive values. (Trallero-Araguás et al., 2012). In contrast to adults, JIIM has no paraneoplastic relationship. (Chiu & Co, 2011). Skin symptoms have a slower start and are more widespread than in other JDM categories. These antibodies have been linked to skin ulcers and lipodystrophy in particular. Unfortunately, this wasn't reported consistently because subsequent studies did not find ulceration or V-rashes to be much more common in this group compared to the others. (Shah et al., 2013). It is worth noting that levels of TIF1 antibodies have been observed to correlate with responsiveness to B-cell depletion treatment in pediatric patients. (Aggarwal, Oddis, Goudeau, Koontz, Qi, & Reed, 2016).

The elevated risk of cancer development has been well-documented, leading to the sub-categorization of cancer-associated myositis (CAM). (Zampieri et al., 2010). Myositis patients have a much greater overall risk of cancer than the general population, and roughly 10% of IIM are connected with malignancy (Felson et al., 2001). In DM, the risk is notably high in the first 5 years following diagnosis. (Maoz et al., 1998). Nasopharyngeal carcinoma and lung, ovarian, pancreatic, stomach, and

colon adenocarcinomas are the most common cancers associated with DM (Zahr & Baer, 2011).

Many studies have suggested that the presence or absence of certain antibodies is a risk factor for malignancy in myositis. The autoantibody profile is thought to be a valuable technique for identifying people at risk of CAM. (Chinoy, Fertig, Oddis, Ollier, & Cooper, 2007). The best-established antibodies in this context are directed against TIF1- with excellent sensitivity and specificity for cancer-associated DM in adult patients. (Hoshino et al., 2010). However, not in JDM (Gunawardena, Betteridge, & McHugh, 2008). Moreover, NXP-2 positivity in DM patients has been linked to an increased risk of cancer. (Fiorentino et al., 2013). The link between anti-synthetase and anti-HMGCR antibodies and cancer is less obvious and requires additional research. In clinical practice, repeated investigations can be indicated in DM patients at risk to exclude an associated malignancy, although precise guidelines on the frequency and duration of such diagnostic procedures are currently lacking.

Figure 1.1 This figure depicts the domain structures of the TIF1 protein family (A) and a detailed view of TIF1-γ (B). Panel (A) shows the organization of TIF1-α, TIF1-β, TIF1-γ, and TIF1-δ, highlighting the RBCC (RING, B-box, coiled-coil) unit, PHD Bromo domain, and other specific functional sites such as the TSS (transcription start site), NR box, and HP1 box, along with their respective positions and percentages of homology. Panel (B) provides an in-depth look at TIF1-γ, illustrating the role of the RBCC unit in ubiquitin ligase activity and protein interactions, and the binding of Smad2/3 and H3/4 histones, highlighting the functional significance of different domains in TIF1-γ.

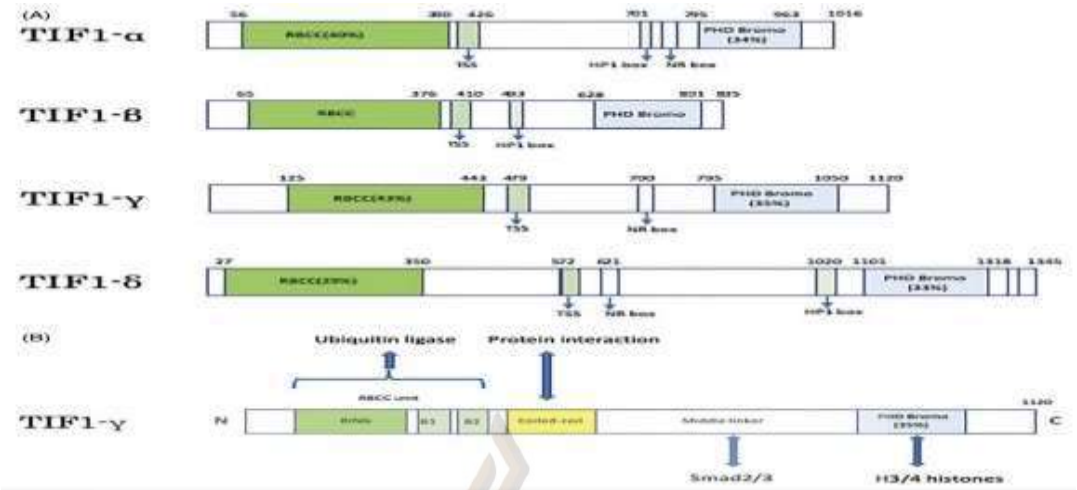

Figure 1.1 This figure depicts the domain structures of the TIF1 protein family (A) and a detailed view of TIF1- γ (B)

Source: Kotobuki, 2020

Figure 1.1 This figure illustrates the roles of TIF1γ in the TGF-β and Wnt signaling pathways. On the left, TGF-β binds to its receptor (TGFβR), leading to phosphorylation of Smad2/3. TIF1γ interacts with these phosphorylated Smads, facilitating their nuclear translocation to regulate gene transcription. TIF1γ also ubiquitinates Smad4, targeting it for degradation. On the right, β-catenin can enter the nucleus and stimulate the transcription of target genes like Cyclin D1 because Wnt signaling stops GSK-3β from breaking it down. TIF1γ also ubiquitinates β-catenin, leading to its degradation and modulation of Wnt signal

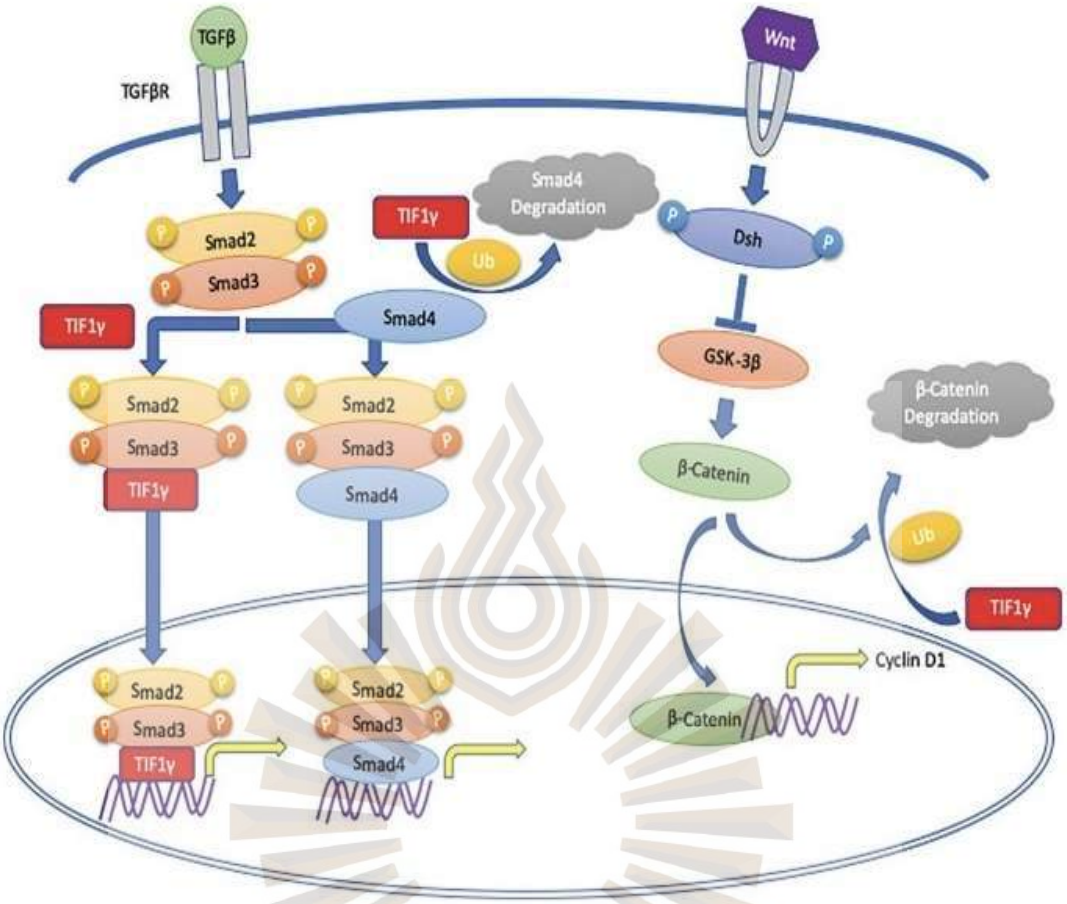

Figure 1.2 This figure illustrates the roles of TIF1γ in the TGF-β and Wnt signaling pathways

Source: Kotobuki, Tonomura, & Fujimoto, 2021

1.2 Research Objectives

1.2.1 Describe the clinical features of dermatomyositis patients with anti-TIF1 gamma positive.

1.3 Research Questions/ Assumptions

What are the classic clinical manifestations of adult dermatomyositis patients with anti-TIF1 gamma positive?

1.4 Research Framework

This study's conceptual framework was developed using the PICO

Patients/Problem – Dermatomyositis patients with anti-TIF1 gamma-positive

Intervention – All type test for detections of anti-TIF1 gamma antibody

Comparison – Dermatomyositis patients without anti-TIF1

Outcome – Clinical characteristics of adult dermatomyositis patients with anti-TIF1 gamma-positive

1.4.1 Hypothesis – Patients with anti-TIF1 gamma positive dermatomyositis have a distinctive clinical phenotype characterized by: • More severe skin manifestations, such as widespread, and heliotrope rash. • Higher risk of dysphagia and • Increased risk of malignancy.

1.5 Definition of Terms

IIM – Idiopathic Inflammatory Myopathies

MSAs – Myositis Specific Antigens

TIF1 γ – Transcriptase Intermediary Factor 1 gamma

MAAs – Myositis-Associated Antibodies

CADM – Cancer Associated Dermatomyositis

DM – Dermatomyositis

CHAPTER 2

LITERATURE REVIEW

Dermatomyositis was originally identified in 1863 when German pathologist Ernst Leberecht Wagner reported a patient with a peculiar skin rash and muscular weakness. Heinrich Unverricht, a German neurologist, recorded a similar case in 1886, and the disease became known as the Unverricht-Wagner syndrome. Georges Potain, a French physician, recorded the first instance of dermatomyositis in Europe in 1887. Gustav Stertz, a German dermatologist, was the first to report the link between dermatomyositis and cancer in 1916. (Keitel & Wolff, 2016).

Dermatomyositis was identified as a unique autoimmune disease in the decades that followed. Anthony Bohan and James B. Peter, two American physicians, categorized dermatomyositis into five categories in 1975, which were used for decades. (Leclair & Lundberg, 2018). Multiple myositis-specific autoantibodies (MSAs) were found and reported in the 1990s. These MSAs are used to distinguish dermatomyositis and other idiopathic inflammatory myopathies because they target various cytoplasmic ribonucleoproteins. (Satoh, Tanaka, Ceribelli, Calise, & Chan, 2017) Dermatomyositis is now a well-known autoimmune illness, yet it is still uncommon. It affects people of all ages, although it is most frequent in adults aged 40 to 60. (Qudsiya & Waseem, 2023).

2.1 TIF1 in Normal Patients Versus Dermatomyositis Patients

TIF1 is one of four TIF1 family members, the others being TIF1. TIF1-protein has been found in normal tissues such as skeletal muscle and skin, and it is implicated in transcriptional control, cell proliferation, apoptosis, and carcinogenesis. TIF1- has been shown to operate as both a tumor suppressor and a tumor promotor in

malignancies, depending on the kind of cancer. TIF1- Ab is an autoantibody that directly interacts with TIF1 and is commonly observed in cancer patients with adult dermatomyositis. It has been shown that cancer is only diagnosed in patients with TIF1- Ab positive 3 years before or 2.5 years after the diagnosis of myositis. (Venturini et al., 1999).

2.2 Skin Manifestations in Patients with TIF1

Patients with anti-TIF1-gamma antibodies had specific dermatological features such as heliotrope rashes, shawl signs, and Gottron's papules, as well as symptoms like dysphagia and truncal weakness. They also had a higher risk of developing cancer and higher mortality rates compared to patients without these antibodies.

A total of 96 dermatomyositis patients were studied, and 36 of them tested positive for anti-TIF1-Ab. Heliotrope rashes, shawl signs, periungual erythema, holster signs, Gottron's papules, dysphagia, and truncal weakness were more common in anti-TIF1-Ab-positive individuals ($P<0.05$). Interstitial lung disease, polyarthritis, cutaneous ulcers, palmar papules, and mechanic's hands were less common ($P<0.05$). After 48 months of follow-up, 63.9% of anti-TIF1-Ab-positive patients developed cancer compared to 8.5% of Ab-negative patients (odds ratio 19.1, 95% confidence range 6.1-59.8; P0.001). The most prevalent cancers were nasopharyngeal carcinoma (NPC) and breast cancer, followed by intestinal, lung, and non-Hodgkin lymphoma. The majority of malignancies (78.3%) developed within 13 months after the initiation of dermatomyositis or 4 months following. Anti-TIF1-Ab-positive individuals had a considerably increased death rate. (Chua, Low, Lim, & Manghani, 2022).

2.3 TIF1 Patients with Hypopigmented Skin Disorder

Cutaneous features in anti-TIF1-gamma positive patients, including palmar hyperkeratotic papules and psoriasis-like lesions. TIF-1 autoantibodies were found in 55 (41%) of the patients. Patients with anti-TIF-1 antibodies were not as likely to

experience systemic symptoms such as Raynaud phenomenon, interstitial lung disease, and arthralgia/ arthritis. TIF-1 autoantibodies resulted in more widespread skin manifestations with some patients exhibiting distinctive signs such as psoriasis-like lesions, palmar hyperkeratotic papules, and a unique finding of hypopigmented and telangiectatic ("red on white") patches. (Fiorentino et al., 2015).

2.4 TIF1 in Patients with Skin Rash and Muscles Weakness

Patients with anti-TIF1-gamma antibodies had a distinctive skin rash and muscle weakness, but no interstitial lung disease. 148 patients were treated with IIM throughout this period, with 9 instances being DM with anti-TIF1g positive. There were four and five patients diagnosed with and without cancer, respectively. The average age upon the beginning of TIF1-DM in 9 individuals was 63 years old. DM with cancer and anti-TIF1 positive patients were substantially older than DM without cancer with anti-TIF1g positive (average: 78.0 vs 57.4). All nine TIF1-DM patients developed a characteristic skin rash and muscular weakness. Dysphagia was present in seven of them. Interstitial lung disease was not found in all TIF1-DM patients. Glucocorticoids (GCs) were given to eight TIF1-DM patients, immunosuppressants to four, and intravenous immunoglobulins (IVIG) to seven. All four CA-TIF1-DM patients were treated with GC. (Fujikawa et al., 2019).

2.5 TIF 1 Patient with a High Risk of Developing Cancer

Dermatomyositis is known to be related to cancer, hence cancer screening is required for DM patients. The cutaneous manifestations of TIF-1 DM patients were extensive, dark red in color, and dispersed across the body. When the cutaneous manifestation is severe, worsened by dysphagia in the absence of ILA, and resistant to corticosteroid treatment, doctors should test TIF-1 antibody levels and conduct cancer screening.

Anti-TIF1 antibodies have been found in DM individuals all over the world since then. Anti-TIF1- antibodies are currently thought to be present in 13-31% of

people with DM and 22-29% of children with DM. Anti-TIF1 antibodies are a powerful predictor of cancer-related DM. In one research, 78% of individuals with anti-TIF1 antibodies had a cancerous condition. Lung, breast, and stomach cancer are highly prevalent malignancies linked with anti-TIF1-DM. The presence of anti-TIF1-antibodies in a DM patient should indicate a complete cancer screening. If cancer is discovered, it is critical to treat it as soon as possible since this might lead to an improvement in DM symptoms. (Harada et al., 2022).

The discovery of anti-TIF1 antibodies in DM was a big step forward in our knowledge of the illness. It shown that DM may be induced by an autoimmune reaction to a particular protein called TIF1-. This finding has resulted in the development of novel DM diagnostic tests and therapies. The discovery of anti-TIF1-antibodies has also aided in the identification of a subset of DM patients who are at high risk of malignancy. This knowledge is significant for physicians because it helps them screen these people for cancer more closely and treat them more quickly if cancer is discovered. (Gunawardena et al., 2008)

Anti-TIF-1 antibodies are more common in research done in the United States and Europe than in those conducted in Asia. Anti-TIF-1 antibody prevalence in DM ranges from 8-41% in the United States and Europe, but just 7-14% in Japan. Women are more likely than males to have anti-TIF1-DM. The typical onset age of anti-TIF1-DM is 50 years. The illness, however, can strike at any age, even youngsters. (Fiorentino et al., 2013)

2.6 Skin Rash in TIF1 Patients with Internal Organ Involvement

Patients with dermatomyositis who have anti-TIF1-gamma antibodies have a more severe form of the illness, with more prominent muscular weakness and skin rash. Internal organ involvement, such as lung disease, heart disease, and arthritis, is also more common in those with these conditions. (Stuhlmüller, Schneider, González-González, & Feist, 2019).

Treatment of dermatomyositis patients with anti-TIF1-gamma antibodies is identical to treatment of DM patients without anti-TIF1-gamma antibodies. Anti-TIF1 antibody-positive DM is treated in the same way as other DMs, such as anti-MDA5 antibody-positive DM and anti-Mi-2 antibody-positive DM. This form of therapy mostly consists of prednisolone and immunosuppressants, although in anti-TIF1 antibody-positive DM patients with malignancies, it has been demonstrated that malignancy treatment should be emphasized. Intravenous immunoglobulin (IVIG) treatment has been shown to be useful in situations with dysphagia and/or steroid resistance. (Kotobuki et al., 2021).

The long-term outlook for DM patients who have anti-TIF1-gamma antibodies is typically poorer than for DM patients who do not have anti-TIF1-gamma antibodies. This is due to the fact that DM patients who have anti-TIF1-gamma antibodies are more prone to develop internal organ involvement and malignancy. (Patwardhan, 2020). Patients with DM who have anti-TIF1-gamma antibodies have a more severe version of the illness. These people are more likely to develop internal organ involvement and malignancy. (Ogawa-Momohara et al., 2018). Early identification and therapy are critical for improving these individuals' prognoses. According to recent research, the majority of patients who achieve a clinical response to malignancy also get a clinical response to dermatomyositis. (Lerman & Richardson, 2019)

More study is needed to understand the underlying pathophysiology of anti-TIF1-gamma antibodies in DM individuals. This study may result in the development of more knowledge for these individuals.

CHAPTER 3

RESEARCH METHODOLOGY

In this study, the clinical characteristics of dermatomyositis patients with anti-TIF1 gamma-positive. A systematic review study will be conducted to investigate the clinical characteristics of dermatomyositis patients with anti-TIF1γ positive.

For this systematic review, the PICO (patients/population, Interventions, Comparison, and Outcome) was used to formulate the research question and this will be used to determine the inclusion and exclusion criteria, keywords, and search terms that will be used in obtaining studies.

Review team

i. Dr. Amadeu Romaldo Ximenes Amaral Mendes, M.D.
ii. Dr. Praneet Sajjachareonpong, M.D.
iii. Dr. Pinnaree Katipatanapong, M.D.

3.1 Population and Samples

The population of studies to be used for this systematic review will depend on the Boolean search of the relevant databases as outlined above and the screening strategy as outlined from 3.1i to 3.1iv below.

3.1.1 Screening stage 1 (screening of titles and abstracts).

This stage will involve manual screening of titles and abstracts from the Boolean search for relevance to the research question.

This will be done by both researchers to reach an agreement as to why articles should be included or expunged based on their titles and abstracts.

Duplicate articles will be sought at this stage.

If an article does not fit in for exclusion based on its title or abstract, it will be noted and added for the second level of screening.

Articles excluded after the initial screening of abstracts will be tabulated and reasons will be given for their exclusion.

This stage will give the initial number of studies after the search. They will be counted, and their total number designated as n2 in the table below following the PRISMA flow diagram.

They will be tabulated according to the databases from which they were retrieved.

3.1.2 Screening stage 2 (retrieval of articles)

In this stage, an attempt will be made to retrieve the full texts of articles (n2) that pass screening stage one.

At this stage articles that were not excluded in the screening stage will be added and their full texts will also be retrieved.

Articles whose full texts are retrieved will be tabulated and counted and designated number n3 in the table below.

Articles whose full texts cannot be retrieved after an exhaustive process will be noted and an attempt will be made to contact the respective authors of these articles via phone or e-mail.

A time frame of one (1) month will be given after which if no response is gotten such articles will be tabulated separately and excluded.

3.1.3 Screening stage 3 (full-text critical review for study quality)

This stage will involve full-text reviews. Articles whose full texts are obtained will be critically analyzed using the Critical Appraisal Skills Programme checklists (CASP). (Wolstencroft et al., 2018). This will ensure the quality of the studies to be included in the final analysis. The appraisal will be done independently by members of the review team.

After ensuring study quality, the articles will be further divided and tabulated into those of good methodological quality to be included in the final list and those perceived to be of poor methodological quality and therefore should be excluded (with reasons).

Those studies deemed to be of poor methodological quality to be excluded will be tabulated and reasons for their consideration as poor will be given.

Studies not in the English language will also be excluded separately.

The two reviewers will meet to further agree or disagree on the quality of the studies and any disagreements will be discussed.

Studies of good methodological quality will be screened based on the inclusion and exclusion criteria set out from the onset. They will be tabulated, and their number designated as n4 in the table below following on the PRISMA flow diagram.

3.1.4 Screening stage 4 (final number of studies)

The final screening process will involve those articles that have passed all the screening stages i.e., are not duplicates, are in the English language, full texts have been retrieved and the study quality has been ascertained to be good using the CASP tool.

The full articles will be subjected to another critical review according to the set-out inclusion and exclusion criteria.

Articles that meet the inclusion criteria will be tabulated and designated as (n5) in the table below following on the PRISMA flow diagram. They will constitute the articles for data extraction and the final analysis in the next stage of this systematic review.

Articles excluded will be tabulated and reasons documented.

The entire screening process will be depicted using the PRISMA 2020 flow diagram. (Critical Appraisal Skills Programme, 2023).

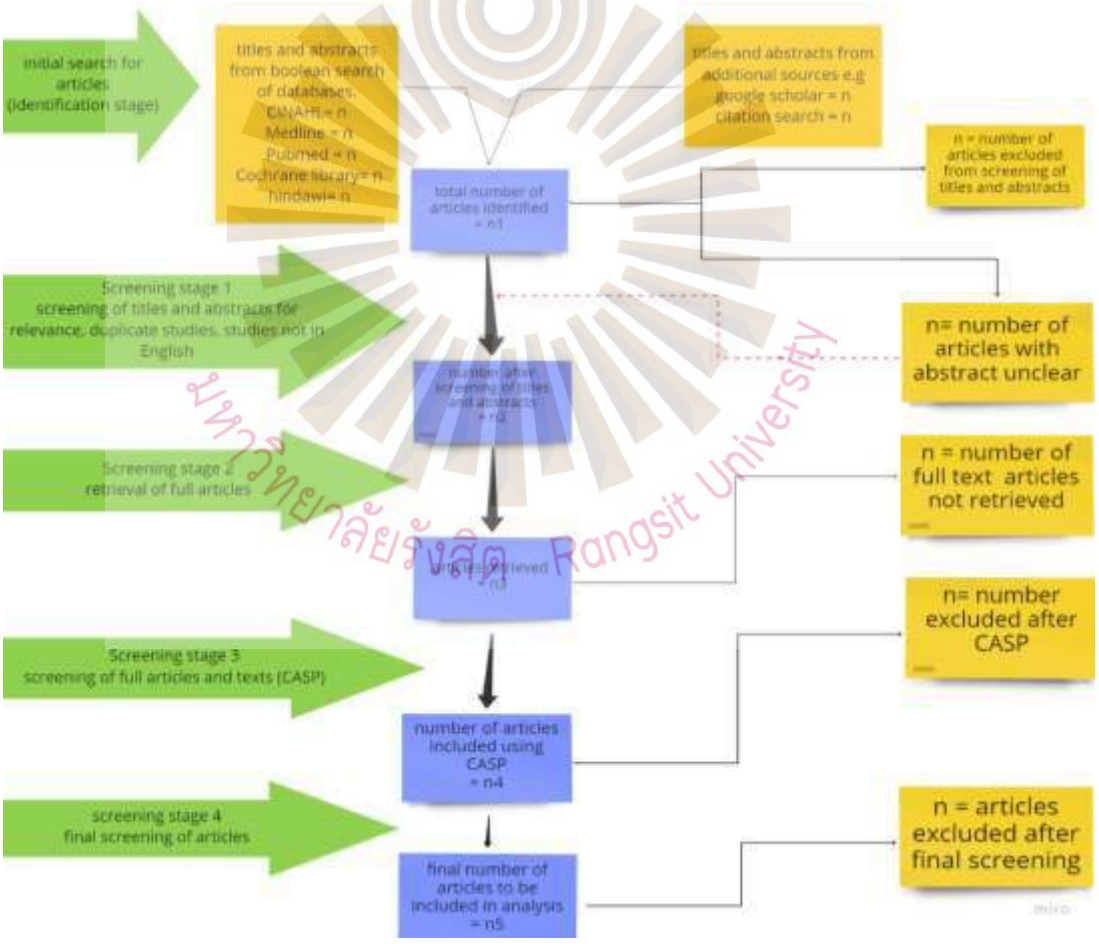

Figure 3.1 Flow diagram of a screening strategy for a population of studies to be included or excluded

Source: Haddaway, Page, Pritchard, & McGuinness, 2020

3.2 Research Instruments

The following research instruments will be used in this study and the format process detail will be attached in appendix xi.

a) The PRISMA 2020 R-package and shiny application – an online application that is specifically designed to help produce PRISMA-compliant flow diagrams. (CASP Checklists., 2023).

b) PRISMA 2020 checklist - This is a checklist form of the PRISMA 2020 guidelines for reporting systematic reviews. Each item of the checklist is explained by the PRISMA 2020 statement paper. (Haddaway et al., 2020).

c) ROBS -2 – The Cochrane collaboration tool for assessing the risk of bias will be used. (Page MJ et al., 2020).

d) Newcastle Ottawa Scale – For observational studies design risk of bias assessment.

e) CASP (Critical Appraisal Skills Programme Checklist).

f) Gradepro software – this is software that can be used to create a summary of finding tables

3.3 Data Collection

3.3.1 Eligibility Criteria

All relevant randomized controlled trials, observational studies (all types), cohort studies, case-control studies, cross-sectional studies, case reports and case series containing dermatomyositis patients with anti-TIF1 gamma positive will be included. As long as they contained the following interventions test for dermatomyositis anti-TIF1 gamma antibody such as ELISA, Immunoblot and others relevant test. We will exclude studies if the controls use animals and are less than 18 years old. Our primary outcome of interest is to determine specific clinical characteristics of dermatomyositis patients with anti-TIF1 gamma positive. Any studies conducted with systematic review and metanalysis will be excluded.

Participants

We will include Dermatomyositis patients with anti-TIF1 gamma positive.

Interventions

We will include all the test for detections of Dermatomyositis anti-TIF1 gamma antibody. Included ELISA and Immunoblot test.

Comparators

We will include Dermatomyositis patients without anti-TIF1 gamma.

Outcomes

We will include the following primary outcome: To determine specific clinical characteristics of dermatomyositis patients with anti-TIF1 gamma positive.

Study design

The following study designs will be included: randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case reports, and case series.

Search strategy

We will include the following in the search string mesh or other subject terms, synonyms, and search filters This search string is constructed by [OR/AND] health librarian. Help to design the search is obtained from [OR/AND] information specialist A peer-review of the search is conducted by [OR/AND] health librarian.

We will search PubMed, Google Scholar, Scopus, and the Cochrane library for cochrane Reviews. Databases are searched from inception up to 13/03/2024 (see Appendix X).

We will apply restrictions to systematic review, metanalysis and all reviews study publication type. We will only include studies in the following languages: English.

Additionally, we manually checked the reference lists of the included studies, performed a backward citation analysis, contacted experts, and used the similar articles feature of a database.

3.3.2 Study selection and screening

Screening

Screening by title and abstract will be conducted by both authors independently. Once the initial title/abstract screening is completed, the full texts of the included studies from that stage will reviewed by both authors to determine if they should be included. After retrieving and screening the full-text stage, both authors will screen the citation search. screens trial registries. Discrepancies will be resolved by both authors.

Data extraction

A standardized form (initially piloted on BLANK-included studies) will be used for data extraction of characteristics of studies, outcomes, and risk of bias. Data extraction will be conducted by the first author. The following data for study characteristics and outcomes are extracted from each included study:

Assessment of the Risk of Bias

The risk of bias will be assessed using the Newcastel Ottawa scale, RoB 2 and ROBINS-1. Depend on type of study design. First authors will assess the risk of bias for each study.

Dealing with missing data

Where data are missing, study investigators or sponsors are contacted via email, after 3 times emailing and if not responded then the result will report not complete data.

3.3.3 Databases to be searched.

The following databases will be searched for the relevant literature to be included in the review.

a) PubMed

b) Scopus

c) Cochrane Library

d) Google Scholar

3.3.4 Search Strings

We will search PubMed, Scopus, The Cochrane Library, and Google Scholar from inception to 13/03/2024 (See appendix X).

Appendix X – search strategies

PubMed- run 30/11/23

("Dermatomyositis"[MeSH Terms] OR "Dermatomyositis"[All Fields]) AND ("Dermatomyositis"[Title/Abstract] AND "anti tif1 gamma"[Title/Abstract]) AND (("ambulatory care facilities"[MeSH Terms] OR ("ambulatory"[All Fields] AND "care"[All Fields] AND "facilities"[All Fields]) OR "ambulatory care facilities"[All Fields] OR "clinic"[All Fields] OR "clinic s"[All Fields] OR "clinical"[All Fields] OR "clinically"[All Fields] OR "clinicals"[All Fields] OR "clinics"[All Fields]) AND ("characteristic"[All Fields] OR "characteristics"[All Fields]))

Scopus - run 1/1/1970

TITLE-ABS-KEY (clinical AND characteristics AND adult AND dermatomyositis AND patients AND with AND anti-tif1 AND gamma) AND PUBYEAR > 2015 AND PUBYEAR <2024 AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (SUBJAREA, "MEDI") OR LIMIT-TO (SUBJAREA, "BIOC") OR LIMIT-TO (SUBJAREA, "NEUR") OR LIMIT-TO (SUBJAREA, "IMMU")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (EXACTKEYWORD, "Adult") OR LIMIT-TO

(EXACTKEYWORD, "Dermatomyositis") OR LIMIT-TO (EXACTKEYWORD, "Human"))

The Cochrane Library
Date Run: 04/12/2023 15:49:07

ID	Search Hits	
#1	MeSH descriptor: [Dermatomyositis] explode all trees	144
#2	(skin and muscles diseases):ti,ab,kw (Word variations have been searched)	1485
#3	(Myositis spesifics autoantibody): ti, ab, kw (Word variations have been searched)	0
#4	(anti-TIF1):ti,ab,kw (Word variations have been searched)	4
#5	(clinical characteristics):ti, ab, kw (Word variations have been searched)	74407
#6	(dermatomyositis):ti,ab,kw (Word variations have been searched)	411
#7	#1 OR #2 AND #6 AND #5 AND #4	144

3.4 Data Analysis

Alternative synthesis methods will be employed utilizing structured reporting after the GRADE of the evidence is carried out.

As a systematic review. The protocol will be initially published on PROSPERO. This is to ensure there is no such review currently going on and to enable peer criticism of the protocol. A search has already been carried out and it has been ascertained that there is no such titled review ongoing. Additionally, any changes made to the protocol will be adequately documented and updated with reasons for such changes.

The PRISMA 2020 reporting guidelines will be used and if need be, there will be modifications to the same. The grade (granding of assessment,

recommendation, development, and recommendation) approach will be used to appraise the quality of evidence and certainty of the outcomes from very low to high based on the risk of bias, inconsistency, indirectness, imprecision, and publication bias. The above will form the basis of the recommendations to be proposed.

A summary of the findings table for the outcomes would then be prepared using the Gradepro application.

The findings from the synthesis of the data will be explained in the discussion section.

Recommendations will be proposed in the conclusion section.

CHAPTER 4

RESEARCH RESULTS

4.1 Demographic Data of Adult DM Patients with Anti-TIF1 Gamma Positive

Table 1 provides important insights into the demographic characteristics, ethnicity distribution, and associated risk factors among adult dermatomyositis patients with anti-TIF1 gamma positivity, as well as the clinical outcomes related to malignancy.

Demographic Characteristics: The study population comprised a total of 261 adult DM patients with anti-TIF1 gamma positivity, with a significant predominance of females (76.6%) compared to males (23.5%). This female predominance aligns with previous observations in dermatomyositis, suggesting a potential gender predisposition to the disease. The median age at symptom onset was 54.2 years, indicating that adult-onset dermatomyositis with anti-TIF1 gamma positivity typically affects individuals in their fifth to sixth decades of life.

Ethnicity Distribution: The majority of patients included in the analysis were of Asian ethnicity (77.4%), followed by Caucasian (21.5%), Latino (2.3%), Pacific Islander (0.8%), and African American (0.4%). These findings highlight the ethnic diversity among adult DM patients with anti-TIF1 gamma positivity, with a higher prevalence observed in Asian populations. However, further research is needed to explore potential genetic and environmental factors contributing to these ethnic disparities.

Associated Risk Factors: Smoking prevalence (24.5.1%) 15 out of 61 patients from 3 cohort studies suggests that a notable proportion of these patients may be at an even higher risk for developing lung cancer due to the combined effects of smoking and their underlying condition. These patients should be closely monitored for early signs of lung cancer. This could involve regular imaging studies and pulmonary function tests. Smoking cessation programs could be particularly beneficial for this subgroup of patients to potentially reduce their risk of lung cancer. Given that patients with anti-TIF1γ positive DM are already at an elevated risk for malignancies, the presence of smoking could potentially amplify the risk of lung cancer in these patients.

Clinical Outcomes: The median duration of follow-up was 48 months, indicating that patients were longitudinally monitored for an extended period. The median time from diagnosis of dermatomyositis with anti-TIF1 gamma positivity to the development of cancer was 4.75 months, with a median age at cancer diagnosis of 61.75 years. This highlights the importance of vigilant surveillance for malignancy in these patients, particularly within the first few months following diagnosis. Furthermore, the median time from diagnosis to death was 8.3 months, underscoring the potentially aggressive nature of anti-TIF1 gamma-positive dermatomyositis, particularly in cases associated with malignancy.

In summary, the results from Table 1 below provide valuable insights into the demographic characteristics, ethnicity distribution, associated risk factors, and clinical outcomes among adult dermatomyositis patients with anti-TIF1 gamma positivity. These findings underscore the need for comprehensive multidisciplinary management approaches, including close monitoring for malignancy and targeted interventions aimed at improving outcomes in this patient population.

Table 4.1 Sociodemographic Data of Adult DM Patients with Anti-TIF1 γ Positive

Total number of sample n=261 from 11 studies	Country*	Total Number of Adult Patients with DM anti-TIF1γ positive: 261	Female 200(76.6%)	Median age, years: 54.2(49.5-68.6)	Ethnicity: Asian 77.4% Caucasian 19.2% Latinos 2.3% African-American 0.4% Pacific-Islander 0.8%	Smoker 15 from 61 (24.5%)	The median time of follow up duration were 48 months (5-75)	The median time diagnosis of DM anti-TIF1 γ until develop cancer 4.75 months (0-24)	median age at Cancer diagnosis 61.75 years (59.5-68.0)	Time from diagnosis to death (median) 8.3 months (4.6-12)
(Fiorentino et al., 2015)	USA	46	39	49.5	Asian 3 Caucasian 33 Latinos 6 African-American 1 Pacific-Islander 2	0	60.0	0	63.5	0
(Chua et al., 2022)	Singapore	36	26	61.5	Asian 36	6	2.5	0(-288-22)	0	12
(Harada et al., 2022)	Japan	14	9	68.6	Asian 14	6	0	18(12-24)	0	0
(Zhang et al., 2022)	China	80	63	52.0	Asian 80	0	4.5	2.0	60.0	0
(Wong et al., 2021)	China	28	19	60.8	Asian 28	0	7.5	0	0	0
(Didona et al., 2020)	German	5	5	45.0	Caucasian 5	0	0	0(-24-24)	60.0	0
(Gupta et al., 2021)	India	8	8	50.0	Asian 8	0	0	0	59.5	0
(Isfort et al., 2021)	USA	1	1	45.0	Caucasian 1	0	3.0	0	0	0
(Ikeda et al., 2020)	Japan	31	21	66.4	Asian 31	0	0	5(0-24)	68.0	0
(Shibata et al., 2019)	Japan	1	0	71.0	Asian 1	0	0	0	0	4.6
(Masiak et al., 2016)	Poland	11	8	54.2	Caucasian 11	3	0	7.5(1-18)	0	0

4.2 Cutaneous and Extracutaneous Manifestation of Adult DM Patient with Anti-TIF1 Gamma

Tables 4.2 and 4.3 provide a comprehensive overview of the cutaneous manifestations, musculoskeletal involvement, pulmonary complications, and outcomes observed in a cohort of 261 adult dermatomyositis (DM) patients with anti-TIF1 gamma positivity.

Cutaneous Manifestations: The majority of patients exhibited characteristic cutaneous manifestations, with the heliotrope rash being the most prevalent (78.0%), followed by Gottron's sign (58.1%) and Gottron's papules (43.1%).

The findings from this table suggested that anti-TIF1 gamma-positive dermatomyositis represented a distinct clinical entity characterized by specific cutaneous manifestations. In contrast, adult dermatomyositis patients lacking anti-TIF1 gamma positivity demonstrated a higher prevalence of symptoms including mechanic's hands, periungual erythema, periungual telangiectasia, Raynaud phenomenon, and calcinosis as documented in the studies conducted by (Fiorentino et al., 2015, p.13; Chua et al., 2022, p.758; Masiak, Kulczycka, Czuszyńska, & Zdrojewski, 2016, p.16.)

Musculoskeletal Involvement: Musculoskeletal symptoms were common among the patients, with myalgia (36.2%), muscle weakness (35.0%) being predominant, and proximal muscle weakness was observed in the largest subset of patients (81.6%), 31 out of 38 patients from 1 cohort studies and 2 case reports. while dysphagia was reported in a significant proportion (42.0%), highlighting the potential impact on functional status and quality of life. In comparison with DM with anti-TIF1 gamma negative, muscle weakness, myalgia, and proximal muscle weakness were also present but less frequent. In one study (Chua et al., 2022, p.758) reported that polyarthritis had more prevalence in adult DM with anti-TIF1 gamma negative.

Dysphagia was evident in both groups, those negative and positive for anti-TIF1 gamma antibodies, yet it was more prevalent in dermatomyositis cases positive for anti-TIF1 gamma.

Furthermore, the substantial proportion of patients with dysphagia highlights the potential impact on swallowing function and the importance of multidisciplinary management involving rehabilitation and nutritional support.

Pulmonary Complications: Interstitial lung disease (ILD) was documented in a notable proportion of patients (14.5%), 32 out of 220 patients from 5 cohort studies. underscoring the importance of pulmonary assessment and surveillance in this population. ILD represents a significant morbidity factor and may contribute to disease severity and prognosis.

The research by (Fiorentino et al., 2015, p.12; Chua et al., 2022, p.758; Wong, So, Lam, & Yip, 2016, p.133) collectively suggest that pulmonary complications were less common among individuals in the anti-TIF1 positive group. However, further investigations are warranted to elucidate this relationship and provide additional insights.

Based on this study ILD were less frequently found in DM with anti-TIF1 gamma positive. A significant subset of patients emphasizes the importance of pulmonary assessment and monitoring to detect early signs of respiratory impairment and guide therapeutic interventions. Additionally, the association between anti-TIF1 gamma-positive dermatomyositis and malignancy underscores the need for vigilant cancer screening protocols and multidisciplinary collaboration involving oncologists and dermatologists.

Table 4.2 Summarize the Cutaneous Manifestations Frequently Seen in Adult DM Patients with Anti-TIF1 γ Positive

Total number of sample n=261 from 11 studies	Heliotrope sign 78%	Gottron sign 58.1%	Gottron's papules 43.1%	V sign 43.1%	Shawl sign 40%	Periungual erythema 36.5%	Facial edema & erythema 31.5%	Holster sign 24.6%	Scalp rash 16.2%	Pruritus 15.4%
(Fiorentino et al., 2015)	78.2%	78%	67%	98%	0%	91%	96%	71%	87%	87%
(Chua et al., 2022)	72.2%	0%	72%	0%	50%	69.4%	0%	22.2%	0%	0%
(Harada et al., 2022)	64%	43%	0%	0%	57%	0%	0%	0%	0%	0%
(Zhang et al., 2022)	91.3%	70%	0%	80%	60%	0%	0%	0%	0%	0%
(Wong et al., 2021)	96.4%	96.4%	96.4%	0%	96.4%	0%	0%	96.4%	0%	0%
(Didona et al., 2020)	100%	0%	60%	0%	40%	0%	0%	0%	20%	20%
(Gupta et al., 2021)	100%	0%	0%	0%	0%	0%	100%	0%	0%	0%
(Isfort et al., 2021)	100%	100%	0%	0%	0%	100%	0%	0%	0%	0%
(Ikeda et al., 2020)	48.4%	80.6%	77.4%	0%	0%	83.9%	90.3%	0%	0%	0%
(Shibata et al., 2019)	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%
(Masiak et al., 2016)	27.2%	9%	0%	36.3%	0%	9%	27.2%	0%	0%	0%

Table 4.3 Summarize the Extracutaneous Manifestations Frequently Seen in Adult DM Patients with Anti-TIF γ Positive

Total number of sample n=261 from 11 studies	Proximal muscle weakness 31 from 38 (81.6%)	Amyopathy 20.4% (53)	Myalgia 36.2% (94)	Muscle weakness 35% (91)	Arthritis / Arthralgia 9.6% (25)	Dysphagia 42% (109)	ILD[1] 12.3% (32)	Highest Creatinine Kinase, median (U/L): 498 (342-17698.5)	Associated with malignancy 45.5% (119)	Mortality 11.2% (29)
(Fiorentino et al., 2015) n=46	0%	26%	0%	0%	36%	37%	5%	342	22%	0%
(Chua et al., 2022) n=36	80.6%	19.4%	0%	0%	0%	41.7%	5.6%	473	63.9%	36.1%
(Harada et al., 2022) n=14	0%	7.1%	21%	64%	0%	71%	0%	-	86%	86%
(Zhang et al., 2022) n=80	21.3%	68.8%	68.8%	0%	46.3%	25%	0%	-	37.5%	0%
(Wong et al., 2021) n=28	0%	35.7%	0%	0%	10.7%	32.1%	21.4%	496	53.6%	0%
(Didona et al., 2020) n= 5	0%	0%	0%	0%	0%	0%	0%	-	40%	0%
(Gupta et al., 2021) n=8	0%	0%	0%	0%	0%	0%	0%	-	50%	0%
(Isfort et al., 2021) n=1	100%	0%	100%	100%	100%	0%	0%	-	0%	0%
(Ikeda et al., 2020) n=31	0%	19.4%	80.6%	80.6%	9.7%	61.3%	12.5%	987.8	51.6%	0%

Table 4.3 Summarize the Extracutaneous Manifestations Frequently Seen in Adult DM Patients with Anti-TIF γ Positive (Cont.)

Total number of sample n=261 from 11 studies	Proximal muscle weakness 31 from 38 (81.6%)	Amyopathy 20.4% (53)	Myalgia 36.2% (94)	Muscle weakness 35% (91)	Arthritis / Arthralgia 9.6% (25)	Dysphagia 42% (109)	ILD[1] 12.3% (32)	Highest Creatinine Kinase, median (U/L): 498 (342-17698.5)	Associated with malignancy 45.5% (119)	Mortality 11.2% (29)
(Shibata et al., 2019) n=1	100%	0%	100%	100%	0%	100%	0%	500	100%	100%
(Masiak et al., 2016) n=11	0%	0%	81.8%	0%	27.2%	36.3%	0%	17698.5	36.3%	27.2%

[1]Interstitial lung disease.

4.3 Type of malignancy based on sex and organ locations affected.

Table 4 provides a detailed breakdown of the organ locations of cancers observed in a cohort of 119 adult dermatomyositis patients with anti-TIF1 gamma positivity, categorized by gender and presented as both raw numbers and percentages.

Cancer Distribution by Organ Location:

Nasopharyngeal cancer was the most common malignancy observed, accounting for 11.8% of total cancer cases for nasopharyngeal cancer with a slightly higher prevalence in males compared to females. Breast and lung cancer were the next most frequent, each comprising 10.9% and 10.1% of total cancer cases, respectively. Notably, breast and lung cancer were observed in female patients. Ovarian cancer accounted for 8.4% of total cancer cases and was also predominantly observed in female patients.

Other less common cancer types included bowel, gastric, non-Hodgkin lymphoma, bladder, uterine, kidney, B-cell chronic lymphocytic leukemia (B-CLL), gallbladder, thyroid, fallopian tube, pancreatic, and esophageal cancers, each representing a smaller proportion of total cancer cases.

Gender Differences:

There were notable gender differences in the distribution of certain cancer types. For instance, nasopharyngeal cancer was more prevalent in males, while breast, lung, and ovarian cancers were exclusively observed in females. This gender disparity may reflect underlying biological differences or environmental exposures.

It's worth noting that some cancer types were observed in both genders, albeit with varying frequencies. For example, bowel and gastric cancers were more common in males, while bladder cancer was observed exclusively in males. Conversely, uterine cancer was only observed in females.

Unknown Organ Location:

A significant proportion (38.7%) of cancer cases were categorized as "unknown" in terms of organ location. This highlights a limitation in the data collection or reporting process, as the specific anatomical site of these malignancies was not documented.

The findings from this table provide valuable insights into the spectrum of malignancies associated with anti-TIF1 gamma-positive dermatomyositis and underscore the importance of comprehensive cancer screening and surveillance in affected individuals. The observation of a diverse range of cancer types affecting various organ systems highlights the multisystem nature of the disease and emphasizes the need for a multidisciplinary approach to patient management.

The gender differences in cancer distribution suggest potential underlying biological and hormonal factors influencing cancer susceptibility in anti-TIF1 gamma-positive dermatomyositis. Further research is warranted to elucidate the mechanistic basis for these observations and to develop targeted screening and prevention strategies tailored to the specific needs of male and female patients.

Additionally, the high proportion of cancers categorized as "unknown" underscores the importance of standardized reporting practices and thorough documentation of clinical data to facilitate more accurate epidemiological studies and improve our understanding of the relationship between dermatomyositis and malignancy. Addressing these limitations will be critical for optimizing patient care and informing clinical decision-making in this complex disease setting.

Table 4.4 Provides a detailed breakdown of the organ locations of cancers observed in a cohort of 119 adult dermatomyositis patients with anti-TIF1 gamma positivity, categorized by gender and presented as both raw numbers and percentages

Total number of sample n=119 from 11 studies	NPC[1]	LC[2]	BC[3]	OC[4]	CC[5]	GC[6]	NHL[7]	BLC[8]	UC[9]	TC[10]	CVC[11]	FTC[12]	KC[13]	Unknown
(Fiorentino et al., 2015) n=10	-	-	-	-	-	-	-	-	-	-	-	-	-	M≠F[14]: 10
(Chua et al., 2022) n=23	M[15]:3 F[16]:3	M:1 F:1	F:6	-	M:1 F:2	-	M:1 F:1	-	-	F:1	F:1	F:1	F:1	-
(Harada et al., 2022) n=14	-	M:1 F:2	F:2	F:1	M:1 F:1	M:1	M:1	-	F:2	-	-	-	-	M:1 F:1
(Zhang et al., 2022) n=30	-	-	-	-	-	-	-	-	-	-	-	-	-	M≠F: 30
(Wong et al., 2021) n=15	M≠F:7	M≠F:4	-	F4	-	-	-	-	-	-	-	-	-	-
(Didona et al., 2020) n=2	-	F2	-	-	-	-	-	-	-	-	-	-	-	-
(Gupta et al., 2021) n=4	-	-	-	-	-	-	-	-	-	-	-	-	-	M≠F: 4
(Isfort et al., 2021) n=0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
(Ikeda et al., 2020) n=16	M:1	M:1	F:4	F:4	M:1 F:1	M:2	-	M:2	-	-	-	-	-	-
(Shibata et al., 2019) n=1	-	-	-	-	-	M:1	-	-	-	-	-	-	-	-
(Masiak et al., 2016) n=4	-	F:1	-	F:1	F:1	M:1	-	-	-	-	-	-	-	-
Total n, % patients with Cancer based on sex	M:4 F:3 M≠F:7 11.8%	M:3 F:6 M≠F:4 10.9%	F:12 10.1%	F:10 8.4%	M:3 F:5 6.7%	M:5 4.2%	M:2 F:1 2.5%	M:2 1.7%	F:2 1.7%	F:1 0.8%	F:1 0.8%	F:1 0.8%	F:1 0.8%	M:1 F:1 M≠F: 44 38.7%

Nasopharyngeal cancer, [2]Lung cancer, [3]Breast cancer, [4]Ovarium cancer, [5]Colon cancer, [6]Gastric cancer, [7]Non Hodgkin's Lymphoma, [8]Bladder cancer, [9]Uterus cancer, [10]Thyroid cancer, [11]Cervix cancer, [12]Falopian tube cancer, [13]kidney cancer, [14]Unknown sex, [15]Male, [16]Female.

Limitations

While analyzing data from the 11 cohort studies, it became evident that some studies lacked complete information regarding treatments administered and specific types of malignancies observed. This limitation hindered the comprehensiveness of the analysis, as the absence of such crucial data restricted our ability to fully explore the associations between treatments, malignancy types, and clinical outcomes among adult dermatomyositis patients with anti-TIF1 gamma positivity. As a result, the interpretation of findings may be influenced by the incomplete dataset, and further research with more comprehensive data collection is warranted to address this limitation and enhance the understanding of this patient population.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

In this study analyzing 261 adult dermatomyositis (DM) patients with anti-TIF1 γ, we observed a predominance of females (76.6%) with a median age of symptom onset at 54.2 years. The majority of patients were of Asian ethnicity (77.4%), with a smaller representation of Caucasian, Latino, Pacific Islander, and African American individuals. Notably, only 5.7% of patients were smokers. The median follow-up duration was 48 months, and the median time from DM diagnosis to cancer development was 4.75 months. The median age at cancer diagnosis was 61.75 years, with a median time from diagnosis to death of 8.3 months. A significant association between anti-TIF1 γ-positive DM and malignancy was observed, with 119 patients (45.5%) developing cancer.

Cutaneous manifestations were frequent, with heliotrope rash (78.0%), Gottron's sign (58.1%), and Gottron's papules (43.1%) being the most common. Musculoskeletal manifestations included proximal muscle weakness (81.6%), amyopathy (20.4%), myalgia (36.2%), and muscle weakness (35.0%). Dysphagia was reported in 42.0% of patients. Interstitial lung disease was present in 12.3% of cases.

The most common malignancies encountered were nasopharyngeal (11.8%), lung (10.9%), and breast cancer (10.1%). Other notable malignancies included ovarian, bowel, and gastric cancers. A considerable proportion of malignancies were categorized as "unknown" in terms of organ location (38.7%).

Across the studies reviewed, it is evident that adult DM patients with anti-TIF1 gamma positivity exhibit a distinct clinical profile compared to DM patients without this antibody. These individuals often present with specific cutaneous features such as the classic heliotrope rash, Gottron's papules, and a higher prevalence of malignancy-associated dermatomyositis. Furthermore, they tend to have a higher risk of internal organ involvement, and malignancies, and a low risk of interstitial lung disease, arthritis, and arthralgia. The association between anti-TIF1 gamma positivity and cancer risk highlights the importance of diligent cancer screening and surveillance in these patients.

Additionally, the prognosis of anti-TIF1 gamma-positive DM patients appears to be less favorable compared to other DM subsets, with higher rates of disease relapse, treatment resistance, and overall mortality. This underscores the need for personalized treatment approaches tailored to the specific needs of these patients, including aggressive immunosuppressive therapy and close monitoring for disease progression and complications.

Overall, the findings from the reviewed cohort studies provide valuable insights into the clinical characteristics and outcomes of adult DM patients with anti-TIF1 gamma antibody positivity. However, further research is warranted to elucidate the underlying mechanisms driving the distinct phenotype observed in these patients and to develop targeted therapeutic strategies aimed at improving their long-term outcomes.

5.2 Recommendations

Based on the conclusions drawn from this study, the following recommendations are proposed for clinicians, researchers, and healthcare policymakers: Enhanced Clinical Recognition: Healthcare providers should be vigilant in recognizing the clinical features associated with anti-TIF1 gamma-positive DM, particularly the characteristic cutaneous manifestations and potential internal organ involvement. Early identification of these patients can facilitate the prompt initiation of appropriate diagnostic and therapeutic interventions.

Individualized Treatment Approaches: Given the unique clinical profile and prognosis of anti-TIF1 gamma-positive DM patients, treatment strategies should be individualized based on disease severity, organ involvement, and specific patients. Aggressive immunosuppressive therapy, including corticosteroids, immunomodulatory agents, and biological therapies, may be warranted in these individuals to achieve disease control and prevent complications.

Multidisciplinary Care: The management of anti-TIF1 gamma-positive DM patients should involve a multidisciplinary team comprising rheumatologists, dermatologists, oncologists, pulmonologists, and other specialists as needed. This collaborative approach allows for a comprehensive assessment, monitoring, and management both dermatologic and systemic manifestations of the disease.

Cancer Screening and Surveillance: Given the increased risk of malignancy associated with anti-TIF1 gamma-positive DM, regular cancer screening and surveillance protocols should be implemented in clinical practice. This may include age-appropriate cancer screening tests, imaging studies, and tumor marker assessments to detect malignancies at an early, potentially curable stage.

For another type of Dermatomyositis specific antigen and negative TIF1 gamma Dermatomyositis should be monitored and follow up and also screening for malignancy as well.

Research Advancements: Future research endeavors should focus on elucidating the pathogenic mechanisms underlying anti-TIF1 gamma-positive DM and identifying novel therapeutic targets. Prospective cohort studies and clinical trials are needed to validate the findings from retrospective analyses and to evaluate the efficacy of targeted treatment approaches in improving outcomes for these patients.

By implementing these recommendations, healthcare providers can optimize the management and outcomes of adult DM patients with anti-TIF1 gamma antibody positivity, ultimately improving the quality of life for individuals affected by this challenging autoimmune condition.

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APPENDICES

NEWCASTLE OTTAWA SCALE

Case Record Form

Newcastle Ottawa Scale assesses the Risk of Bias for cohort and case-control studies of Clinical Characteristics of Adult Dermatomyositis with anti-TIF1gamma positive.

Table 1 Methodological quality of studies included in the final analysis based on the Newcastle–Ottawa Scale to assess the quality of case–control(n=2) and cohort studies (n=7)

	Selection				Comparability		Outcome		
Cohort studies	Representativeness of the exposed cohort	Non exposed cohort	Ascertainment of exposure	Outcome of interest was not present at the start of the study	Control of important and additional factors	Assessment of outcome	Follow up long enough for the outcome to occur	Adequacy of follow up of cohort	Total
Fiorentino et al. 2015	1	1	1	1	2	1	1	1	9/9
Chua et al. 2022	1	1	1	1	2	1	1	1	9/9
Zhang et al. 2022	1	1	1	1	2	1	1	1	9/9
Wong et al. 2020	1	1	1	1	2	1	0	0	7/9
Masiak et al. 2016	1	1	1	1	2	1	0	0	7/9
Didona et al. 2023	1	1	1	1	2	1	1	1	9/9
Ikeda et al. 2020	1	1	1	1	2	1	1	1	9/9
Harada et al. 2022	1	1	1	1	2	1	1	1	9/9
Gupta et al. 2021	1	1	1	1	2	1	0	0	7/9

*Each study can be awarded a maximum of 1 star for each numbered item within the selection and exposure categories, and a maximum of 2 stars for the comparability category.

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