

CASE REPORT

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# A rare intersection: squamous cell carcinoma of the tonsil and the anti-TIF1 syndrome masquerade

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## Abstract

**Background** Dermatomyositis is a chronic inflammatory condition affecting muscles and skin, often associated with an increased risk of cancer. Specific autoantibodies, including anti-TIF1 (Transcription Intermediary Factor 1), have been linked to this risk. We present a case of dermatomyositis in a male patient positive for anti-TIF1 antibodies, subsequently diagnosed with squamous cell carcinoma of the tonsil, a novel association not previously documented. Early recognition of such associations is crucial for timely intervention and improved outcomes in these patients.

**Case presentation** A 53-year-old Caucasian male with hyperlipidemia presented with chronic dry, scaly skin and pruritus, diagnosed with eczematous dermatitis. Despite treatment, symptoms persisted. After two years, he reported increased redness of the rash and new eruptions on his hands and fingers. During a rheumatology visit, he reported weight loss, fatigue, muscle weakness, and trismus. Further evaluation indicated signs of dermatomyositis, and laboratory tests revealed anti-TIF1 antibodies, prompting further investigation. The patient underwent age-appropriate cancer screening, and due to a known association with malignancy, a positron emission scan was ordered, detecting increased activity in the right tonsil. Subsequent magnetic resonance imaging showed a suspicious mass in the tonsillar area. A biopsy confirmed invasive squamous cell carcinoma positive for P16+. Initial treatment included radiotherapy, with a post-treatment PET scan showing no evidence of disease. However, four months later, the cancer recurred, leading to significant symptoms and complications. Despite supportive measures, the patient succumbed to high-volume oral cavity bleeding during hospitalization.

**Conclusions** TIF1 dermatomyositis is a unique subset of dermatomyositis with a strong association with malignancy, particularly squamous cell carcinoma (SCC). Mechanisms connecting TIF1 dermatomyositis and cancer involve gene expression dysregulation and chronic inflammation. Anti-TIF1 antibodies are key biomarkers, with IgG2 isotype levels highly predictive of cancer risk. Common malignancies include ovarian, breast, and lung cancers, often detected within three years of dermatomyositis onset. Distinctive features include severe skin lesions, dysphagia, and minimal interstitial lung disease. Management focuses on early cancer detection and treatment, with options for refractory disease, including IVIg, rituximab, and emerging therapies like JAK inhibitors. Our case highlights a new association between TIF1α antibodies and tonsil squamous cell carcinoma. Despite successful radiotherapy, cancer recurred. TIF1 antibody detection should prompt rigorous cancer screening, emphasizing multidisciplinary management.

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**Keywords** Dermatomyositis, Anti-TIF1, Squamous cell carcinoma, Tonsil

## Introduction

Dermatomyositis (DM) is a chronic inflammatory condition affecting both muscles and skin, characterized by muscle weakness primarily in the proximal extremities and distinctive skin lesions, including Gottron papules, a heliotropic rash, and the shawl sign. Notably, individuals with dermatomyositis face a significantly heightened risk of developing cancer, with studies indicating up to a 4.66-fold increase in risk compared to the general population [1]. The incidence of malignancy in dermatomyositis patients varies widely, ranging from 5.5 to 42%, and cancer can manifest before, concurrently with, or after the diagnosis of dermatomyositis [2, 3].

A key diagnostic feature of dermatomyositis is the presence of specific circulating autoantibodies that include myositis-specific antibodies such as anti-Jo-1, anti-PL-7, anti-PL-12, anti-MDA5, anti-Mi-2, anti-SRP, anti-TIF1, anti-NXP2, anti-SAE as well as myositis-associated antibodies like anti-PM/Scl, anti-Ku, and anti-Ro, anti-La, anti-U1-RNP, and anti-U3-RNP. These autoantibodies not only aid in diagnosing the condition but also serve as predictors of disease progression and response to treatment. Extensive studies have also proven to establish an association between the presence of certain autoantibodies and an increased risk of malignancy in patients with dermatomyositis [4].

Among these antibodies, anti-TIF1 (Transcription Intermediary Factor 1) antibodies have the strongest correlation, with the risk of malignancy being 9.37-fold higher in patients with anti-TIF1 antibodies [5]. This association was further underscored by a comprehensive cohort study involving 213 individuals with dermatomyositis, revealing a notable rise in cancer frequency from 5% in antibody-negative patients to 18% in those testing positive for anti-TIF1 antibodies [6]. The risk of cancer is notably high in Anti-TIF1 antibodies positive patients approaching the ages of 40 and above, as well as during the period proximate to, more specifically, within 3 years before and after, the diagnosis of dermatomyositis [7]. Moreover, detecting anti-TIF1 autoantibodies has a high sensitivity and specificity (52% and 92%, respectively) in diagnosing cancer in dermatomyositis patients [6]. Hence, these antibodies can be utilized to diagnose as well as stratify the risk of cancer in these patients.

In our report, we detail a case of dermatomyositis in a male patient who exhibited positivity for anti-TIF1 antibodies and was subsequently diagnosed with squamous cell carcinoma of the tonsil. This unique association has not been previously documented, highlighting the importance of vigilant monitoring and early intervention in dermatomyositis patients, particularly those

with identified cancer risk factors such as specific autoantibodies.

## Case presentation

A 53-year-old Caucasian male with a history of hyperlipidemia presented to his primary care physician complaining of chronic dry, scaly skin with pruritus mainly affecting his arms, shoulders, back, face, and scalp. He received a diagnosis of chronic eczematous dermatitis and was prescribed daily application of 0.1% triamcinolone cream along with hydroxyzine. Despite compliance with the treatment regimen, his symptoms persisted. After two years, he returned to the clinic, reporting increased redness around the rash on his neck and face, as well as new skin eruptions on his hands and fingers, for which he had been using over-the-counter emollients. A dermatology evaluation identified a notable antinuclear antibody titer of 1:320 with a speckled immunofluorescence pattern, though it did not reflex. The patient, however, did not meet the classification criteria for lupus. A subsequent biopsy revealed increased dermal mucin when stained with colloidal iron despite negative results from direct immunofluorescence. This finding raised the suspicion of connective tissue diseases, prompting a referral to a rheumatology clinic.

During the rheumatology visit, the patient reported significant 50-pound weight loss, fatigue, difficulty opening his mouth, and muscle loss in his shoulders and legs. He denied current fevers, chills, dyspnea, oral ulcers, alopecia, sicca symptoms, Raynaud symptoms, or lymphadenopathy. Physical examination revealed a maculopapular rash across the shoulders, upper arms, upper back, neck, and torso, consistent with erythema often seen in dermatomyositis, including the “shawl sign.” A macular eruption was also observed over the metacarpophalangeal and proximal interphalangeal joints, suggestive of Gottron’s papules. There was a slight decrease (4/5) in the strength of the proximal upper and lower extremities.

The patient had no significant past medical history and denied a family history of lupus or other autoimmune diseases. Due to concerns of dermatomyositis, further testing was performed. Laboratory tests, including a complete blood count, complete metabolic panel, creatine kinase, and aldolase, were all within normal limits. Magnetic resonance imaging (MRI) of the bilateral lower extremities did not show inflammation. Autoimmune tests, notably the myomarker panel, revealed positive anti-Sjogren’s-syndrome-related antigen A and anti-TIF1 antibodies. Treatment commenced with hydroxychloroquine 200 mg bid, mycophenolate 1000 mg bid,

and prednisone 60 mg daily for six weeks, followed by gradual tapering.

The patient underwent age-appropriate cancer screening. Due to the association of TIF-1 with malignancy, a whole-body positron emission tomography (PET) scan was performed, which showed increased uptake in the right tonsil. Concurrently, the patient was referred to an otolaryngologist due to a few month history of trismus. An MRI of the neck with contrast revealed a concerning parapharyngeal space/tonsil mass (Fig. 1). A panendoscopy was performed, and a biopsy of the right tonsil confirmed invasive squamous cell carcinoma positive for P16+. He underwent the first dose of chemotherapy with high-dose cisplatin; however, it was complicated by prolonged thrombocytopenia. Further, due to an episode of port-related sepsis, the patient declined further chemotherapy despite plans to switch to weekly cisplatin, completing the course of radiotherapy instead. A post-treatment PET scan did not show any evidence of disease, revealing a complete metabolic response to treatment and resolution of F-18 fluorodeoxyglucose (FDG) avidity within the right tonsil and neck (Fig. 2).

Four months later, the patient returned to the emergency department with hemoptysis, worsening trismus, and otalgia. He struggled with mouth opening, could only tolerate liquid supplements, experienced weight loss, and found managing secretions unbearable. Throat examination revealed a large base of tongue mass. PET scan showed moderate to intense FDG activities along the entire right oropharyngeal and hypopharyngeal superficial wall, inferiorly reaching the right vallecular region, suggesting recurrence (Fig. 3). The patient underwent elective tracheostomy and percutaneous endoscopic gastrostomy feeding tube placement but unfortunately

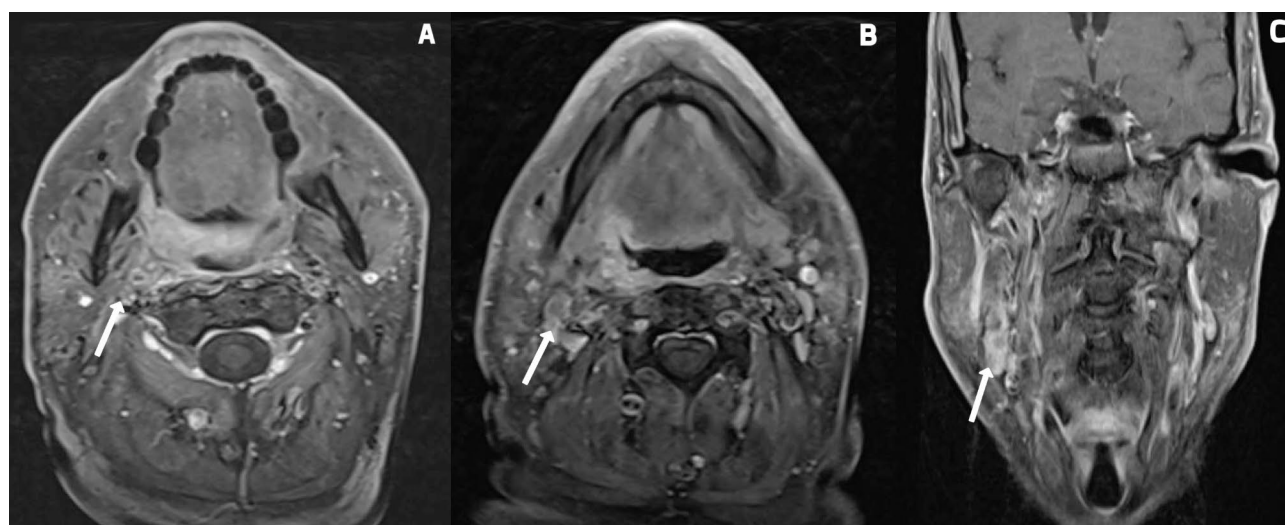
succumbed to complications of high-volume oral cavity bleeding during hospitalization.

## Discussion

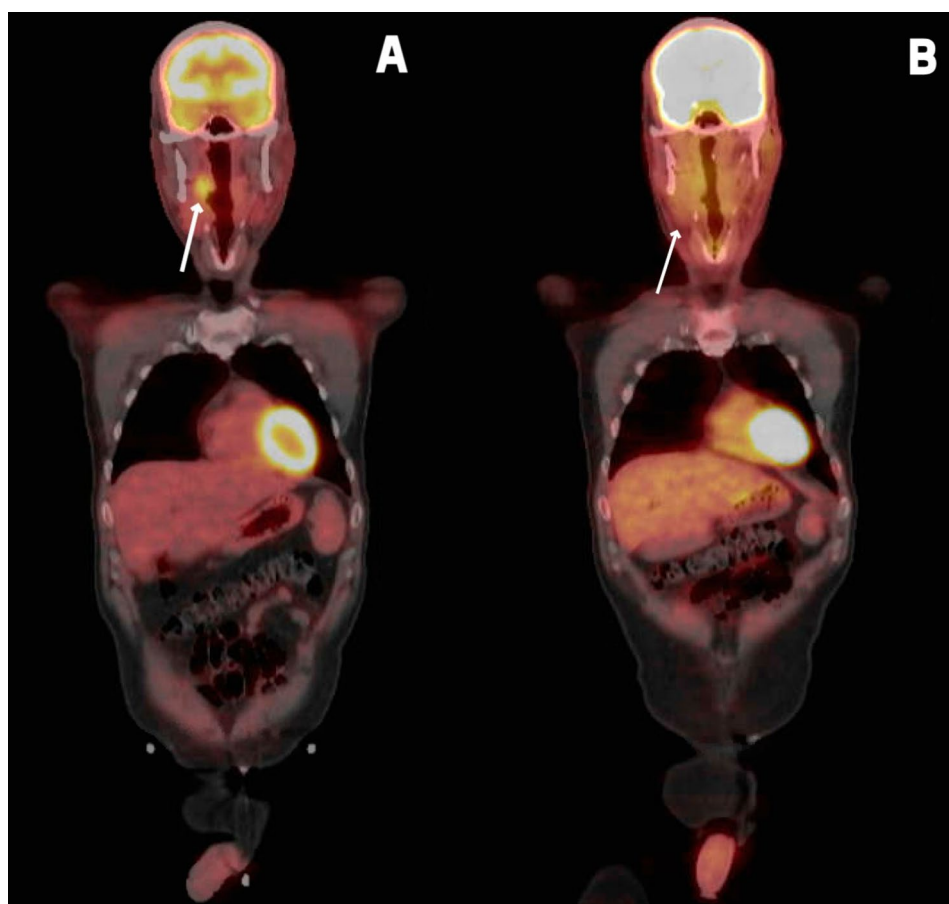
TIF1 $\alpha$  dermatomyositis, also referred to as anti-p155/140 dermatomyositis, is a distinct form of dermatomyositis characterized by the presence of antibodies against a protein called transcription intermediary factor 1 $\alpha$ . This subset has garnered increasing attention due to its unique clinical and serological features, posing diagnostic and therapeutic challenges for clinicians.

Research indicates a significant link between TIF1 alpha dermatomyositis and the development of malignancies, particularly in adults. A retrospective analysis by Fiorentino et al. revealed that patients with TIF1 alpha autoantibodies had a higher risk of developing cancer compared to those without this specific autoantibody [8]. Yang et al. demonstrated a strong statistical association ( $P < 0.001$ ) between these antibodies and cancer in DM patients [9]. Aussy et al. identified the IgG2 isotype of anti-TIF1- $\gamma$  as highly predictive of malignancy, with a 100% positive predictive value when fluorescence intensity exceeded a specific threshold [10]. Cordel et al. further supported the role of anti-TIF1- $\gamma$  IgG2 as a malignancy biomarker [11]. Ogawa-Momohara et al. noted that malignancies in anti-TIF1- $\gamma$ -positive patients tend to be more advanced and diagnosed closer to DM onset compared to those without these antibodies [12]. A meta-analysis by Best et al. confirmed these findings, reporting a diagnostic odds ratio of 9.37 for cancer risk in adult DM patients with anti-TIF1- $\gamma$  antibodies [5].

This association is not limited to a particular type of cancer, as cases have been documented with various malignancies. Prevalent neoplasms encompass ovarian,



**Fig. 1** MRI depicting a 2.9×2.8×5.2 cm ill-defined soft tissue in the right oropharynx (palatine tonsillar region) with extension into the parapharyngeal fat (A), right glossotonsillar sulcus (B) and right level II lymphadenopathy (C)



**Fig. 2** PET scan showing the focus of intensely FDG uptake in the region of the right palatine tonsil (A). PET scan showing resolution of the previously noted right tonsillar FDG avid focus and normalized FDG uptake for the ipsilateral level II FDG avid lymph node, suggestive of complete metabolic response to therapy (B)

breast, lung, gastric, and colorectal tumors, alongside lymphomas in dermatomyositis, lung and urinary bladder cancers, and lymphomas in polymyositis. Cancer can manifest before, concurrently with, or after the onset of dermatomyositis, with detection typically occurring within three years of a DM diagnosis. However, a significant number of cases may be diagnosed within the first year, showing a more rapid progression [13].

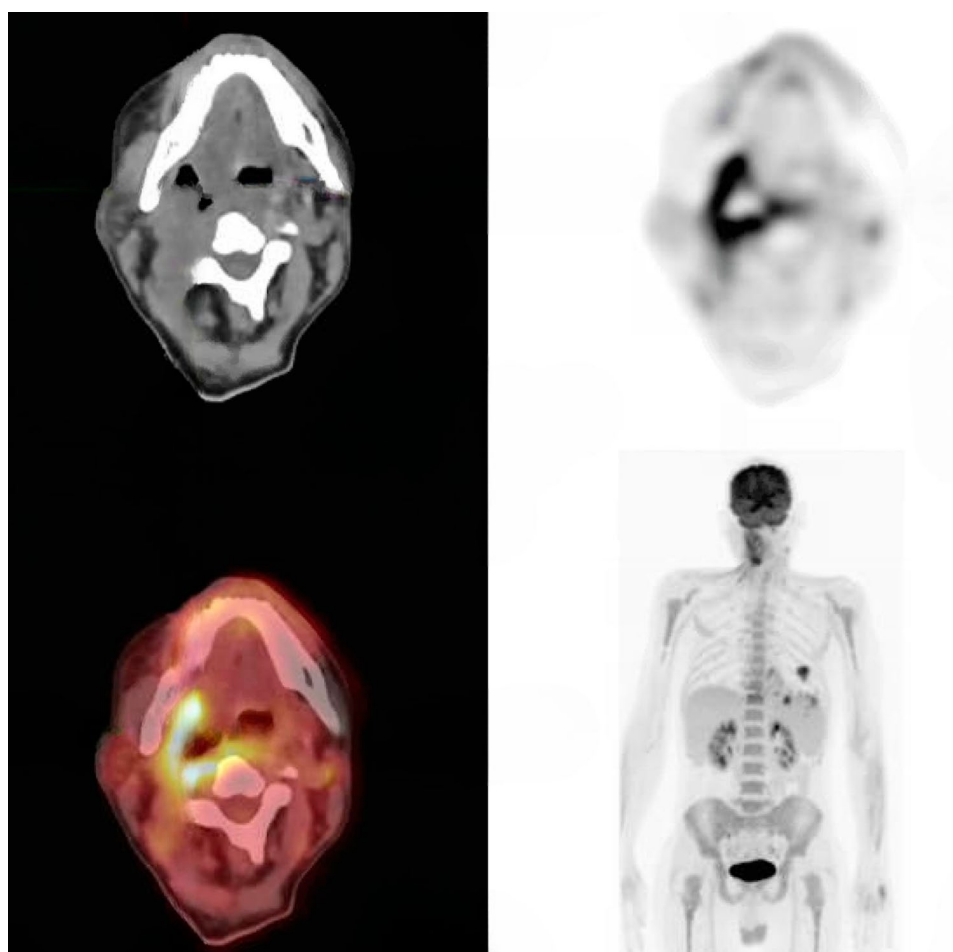
The exact mechanisms linking TIF1 alpha dermatomyositis to malignancy remain elusive, but there are plausible hypotheses. TIF1 alpha plays a role in regulating gene expression and maintaining cellular homeostasis. Aberrant expression or dysregulation of TIF1 alpha may lead to unchecked cell growth and a higher propensity for malignancy. Additionally, the chronic inflammatory state associated with dermatomyositis may contribute to the initiation and progression of malignancies.

Cutaneous findings in anti-TIF-1 antibody-positive dermatomyositis are distinctive and often extensive. These include hallmark rashes such as heliotrope rash and Gottron's papules, as well as the V-neck and shawl signs. Additional features include nailfold telangiectasia,

psoriasis-like lesions, palmar papules, and hypopigmented telangiectatic patches described as “red on white” [14]. These palmar papules show hyperkeratosis and verruca-like structures, unlike the erythematous and tender palmar papules typically associated with anti-MDA5 antibodies [15].

Systemic symptoms such as dysphagia and muscle weakness are common, with oropharyngeal musculature involvement and respiratory dysfunction due to weakened respiratory muscles emerging as distinctive neurological features [16]. Unlike other DM subgroups, individuals with anti-TIF1γ antibodies typically experience lower rates of interstitial lung disease and Raynaud phenomenon [17–18]. A study by Harada et al. highlighted that patients with TIF1γ-positive DM had more severe skin lesions compared to TIF1γ-negative cases, often accompanied by dysphagia. These lesions are notable for their extensive spread, darker pigmentation, and resistance to treatment [14]. Recognizing these features is critical, especially given the strong malignancy association in this subgroup [18].





**Fig. 3** PET scan shows moderate to intense FDG activities along the entire right oropharyngeal and hypopharyngeal superficial wall, inferiorly reaching the right vallecular region, indicating recurrence

In terms of treatment, addressing malignancies takes top priority. Treatment options for steroid-resistant dermatomyositis include high-dose corticosteroids as first-line therapy. For insufficient responses, methotrexate and azathioprine are used as steroid-sparing agents, although their effectiveness as monotherapy is limited [19, 20]. IVIg, particularly Octagam 10%, is FDA-approved for adult dermatomyositis based on positive trial results [19–21]. Rituximab has shown promise in refractory cases, despite its largest trial not meeting primary endpoints [21, 22]. Calcineurin inhibitors like tacrolimus and cyclosporine are effective in cases with antisynthetase syndrome or interstitial lung disease, often in combination with glucocorticoids and cyclophosphamide for severe lung involvement [23, 24]. Emerging options include JAK inhibitors and mycophenolate mofetil, particularly for refractory skin disease [21].

The association between TIF1 $\gamma$  DM and SCC is influenced by several risk factors and predictors. The IgG2 isotype of anti-TIF1 $\gamma$  antibodies has a high positive predictive value for malignancy, especially when levels are

elevated [10, 11]. Risk increases with age, particularly in patients over 60 years, and male sex further heightens susceptibility [10, 25]. Clinical features such as dysphagia, heliotrope rash, and V-neck rash have been associated with malignancy risk in these patients [9]. To reduce diagnostic delays and improve outcomes in patients with anti-TIF1 $\gamma$  dermatomyositis, annual cancer screenings tailored to the patient's age, sex, and clinical profile are crucial for early malignancy detection, especially for SCC, given the strong association between them. Close and consistent monitoring through frequent follow-ups facilitates the early identification of subtle malignancy-related symptoms, allowing for timely and appropriate medical intervention.

Tonsillar SCC is a rare malignancy linked to dermatomyositis in the medical literature. Adi et al. reported a case where dermatomyositis preceded the clinical onset of tonsillar SCC by over a year as a paraneoplastic syndrome, while Kim et al. documented the first two cases in Korea, highlighting the rarity of this association, and Botsios et al. described cases of Caucasian patients

with dermatomyositis linked to pharyngeal malignancies, including tonsillar carcinoma [26–28]. However, the association between anti-TIF1 subtype and tonsillar SCC has not yet been reported, and our case contributes to the existing literature by highlighting this association. Despite completing radiotherapy upon diagnosis, the cancer recurred shortly afterward, even after demonstrating complete resolution in the last PET scan. The identification of TIF1 antibodies in patients with dermatomyositis should trigger meticulous cancer screening protocols. This underscores the critical need for a multidisciplinary approach involving dermatologists, rheumatologists, and oncologists in the comprehensive management of such cases.

# Abbreviations

Anti-TIF1	Anti-Transcription Intermediary Factor 1
MRI	Magnetic resonance imaging
PET	Positron emission tomography
FDG	Fluorodeoxyglucose

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Not applicable.

# Author contributions

MS, SD, and ML wrote the main manuscript text; MS and MT prepared Figs. 1, 2, and 3. MT wrote the abstract and edited the whole manuscript. All authors read and approved the final manuscript.

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# Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

# Declarations

# Ethical approval

Not required for a case report.

# Consent for publication

Written informed consent for publication of identifying images or other personal or clinical details was obtained from the next of kin.

# Competing interests

The authors declare no competing interests.

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