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Amyopathic dermatomyositis with TIF1γ positivity treated with intravenous immunoglobulin

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Abstract

Dermatomyositis is an inflammatory myopathy involving the skin that typically affects patients between 40-60 years of age and is more likely to be diagnosed in women. Around 10-20% of dermatomyositis cases present with subclinical or absent muscle involvement, termed "clinically amyopathic." Presence of anti-transcription intermediary factor 1γ (TIF1γ) antibodies is an important indicator of underlying malignancy. We present a patient with anti-TIF1γ-positive amyopathic dermatomyositis associated with bilateral breast cancer. The patient was safely treated with trastuzumab for breast cancer and intravenous immunoglobulin for dermatomyositis.

Keywords: amyopathic, cancer, dermatomyositis, immunoglobulin, intravenous, IVIG, TIF1γ, trastuzumab

Introduction

Dermatomyositis is an inflammatory myopathy involving the skin with an incidence of approximately one in 100,000 [1]. Characteristic cutaneous findings include a periorbital heliotrope rash, violaceous papules overlying the knuckles (Gottron sign), and an erythematous rash distributed over the neck, upper back, shoulders, and chest (shawl sign), [2]. The disease typically affects patients between 40-60 years of age and is more likely to be diagnosed in women [1]. About 10-20% of dermatomyositis is "clinically amyopathic" and presents with subclinical or absent muscle involvement [1,3]. We herein present a patient with amyopathic dermatomyositis associated with cancer, safely treated with trastuzumab for breast cancer and intravenous immunoglobulin (IVIG) for dermatomyositis.

Case Synopsis

A woman in her 60s with a history of scleroderma and non-small cell lung cancer presented to her primary care physician with an erythematous, pruritic rash on her face, arms, hands, chest, and back for one month. Her scleroderma initially manifested in adolescence with Raynaud phenomenon and digital ulcers whereas her lung cancer was diagnosed in her 50s; both are currently in remission. The patient's scleroderma was well-controlled at the onset of her lung cancer without a photodistributed dermatitis. She was prescribed topical corticosteroids without improvement and referred to a dermatologist, who prescribed a prednisone taper starting at 50mg daily. Her rash relapsed after the taper finished. Three months after the onset of her rash, the patient visited her rheumatologist, who prescribed prednisone 20mg daily and urgently referred her to our dermatology clinic.

Examination revealed brightly erythematous-to-violaceous periorbital plaques (**Figure 1A**). Other characteristic cutaneous findings of dermatomyositis observed in the patient included flat-topped papules on the dorsal metacarpophalangeal joints with periungal telangiectasias and scaling, photodistributed erythematous-to-violaceous papules on the upper trunk and arms, erythematous scaling plaques on the

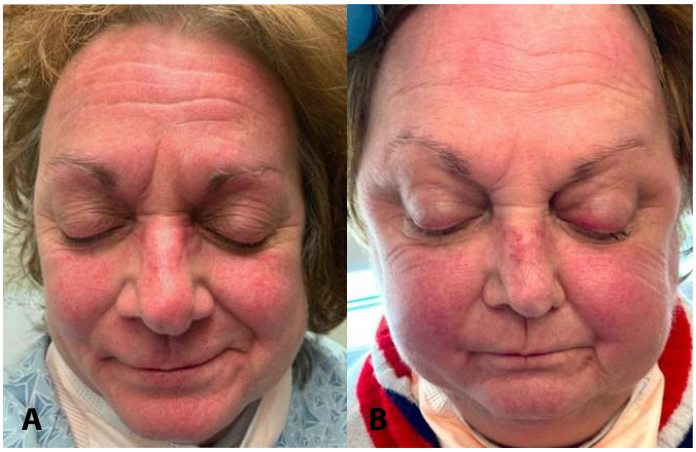

Figure 1. *Characteristic facial findings of dermatomyositis.* ***A)*** *Violaceous periorbital plaques (heliotrope rash).* ***B)*** *Heliotrope rash following 6 months of immunosuppression therapy.*

scalp, and oral ulcerations (not shown). The patient did not experience recent fever, weight loss, or muscle weakness. She had normal muscle strength on examination. Laboratory tests revealed anti-nuclear antibody titers of 1:160, serum aldolase 9.2U/L (normal <7.7U/L), and positive anti-transcription intermediary factor 1γ (TIF1γ) antibody. The remaining myositis panel, including anti-PL7, anti-PL12, anti-Jo1, anti-Mi2, anti-EJ, anti-OJ, anti-SRP, anti-MDA5, anti-NXP2, anti-PM/Scl, anti-U1RNP, anti-U2snRNP, anti-U3RNP, and anti-Ku were negative. Anti-dsDNA, anti-SSA/SSB, complete blood count, C3/C4 complement, and creatinine kinase were also unremarkable.

Skin biopsies of the chest obtained for histopathology demonstrated vacuolar interface dermatitis with scattered dyskeratotic keratinocytes (**Figure 2A**). There was basement membrane thickening and a superficial perivascular infiltrate of lymphocytes, supporting a connective tissue disease (**Figure 2A**). On direct immunofluorescence, intermittent granular basement membrane deposits

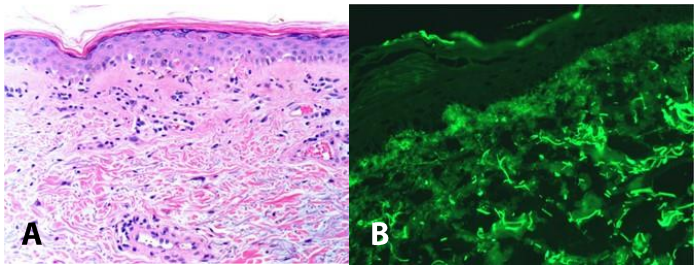

Figure 2. *Tissue histology obtained from the chest.* ***A)*** *H&E, 20×;* ***B)*** *direct C3 immunofluorescence, 20×.*

of IgM, C3, and fibrin were visualized (**Figure 2B**). Together with the characteristic heliotrope rash, Gottron sign, shawl sign, elevated serum aldolase, and anti-TIF1γ positivity, the diagnosis of amyopathic dermatomyositis was confirmed. The presence of anti-TIF1γ positivity was concerning for underlying malignancy, which prompted an urgent workup. Due to the patient's surgical history of total abdominal hysterectomy with bilateral salpingo-oophorectomy, transvaginal ultrasound was not performed. The patient was receiving regular screening computed tomography (CT) for her history of lung cancer with negative findings on her most recent CT scan. Therefore, she underwent positron emission tomography-computed tomography (PET-CT), which revealed metabolically active foci in both breasts. Diagnostic mammography and magnetic resonance imaging supported the presence of abnormal imaging enhancement in both breasts. Breast biopsy confirmed a diagnosis of ER+/PR+/HER2+ bilateral invasive ductal adenocarcinoma.

The patient's breast cancer was treated with bilateral mastectomy and adjuvant chemotherapy, including trastuzumab, a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) protein. For her dermatomyositis, the patient received azathioprine 50mg twice daily, prednisone 50mg daily followed by a slow taper, and monthly IVIG infusions at 2g/kg bodyweight given over two days. At follow-up appointment 6 months later, the patient's rash had substantially improved and she tolerated her immunosuppressive regimen without significant complication (**Figure 1B**). Diagnostic mammography status post bilateral mastectomy revealed no evidence of malignancy.

Case Discussion

Dermatomyositis has a strong association with underlying malignancy; therefore, screening for cancer is crucial once the diagnosis is established. There is an approximate 6-fold elevated risk of underlying malignancy in dermatomyositis and cancer is detected in 9-32% of patients within 3-5 years of diagnosis [2,4]. The most common cancers associated with dermatomyositis are ovarian, breast,

lung, colorectal, melanoma, and non-Hodgkin lymphoma [2]. Although lung cancer is the malignancy most frequently associated with dermatomyositis, breast cancer in women is most commonly associated with the amyopathic subtype of dermatomyositis [5]. Transvaginal ultrasound is typically recommended in adult women to identify a potential ovarian cancer; it was not performed in our patient due to her surgical history [3]. Screening for other possible cancers driven by patient age, sex, and medical history should also be pursued after diagnosis of dermatomyositis [3]. In the case of our patient, a PET/CT comprised the initial work-up. Although based on expert opinion, many dermatologists and rheumatologists who specialize in dermatomyositis recommend PET/CT as the primary malignancy screening modality in patients with TIF1γ positivity owing to the increased risk of malignancy compared to traditional dermatomyositis [6]. PET/CT has the added value of diagnosing a potentially lethal malignancy with one test rather than referral for multiple radiology and specialty studies [7]. When the PET/CT demonstrated metabolically active foci in both breasts, additional imaging including mammography and magnetic resonance imaging were performed prior to biopsy.

Presence of anti-TIF1γ antibodies is an important indicator of underlying malignancy in dermatomyositis. One study identified antibody positivity in over 50% of dermatomyositis patients with concomitant cancer [8]. Hida and colleagues found that patients with anti-TIF1γ positive dermatomyositis had a cancer detected before or within one year of dermatomyositis diagnosis [9]. The association between anti-TIF1γ antibody positivity and amyopathic dermatomyositis remains unclear. A recent study found that all patients with amyopathic dermatomyositis in their cohort lacked anti-TIF1γ positivity, but the sample size (N=3) was too small to conclude whether the amyopathic subtype is differentially associated with presence of this autoantibody [10]. Nevertheless, presence of anti-TIF1γ antibodies should prompt physicians to urgently pursue malignancy work-up as was performed for this patient.

For treatment of HER2+ breast cancer, treatment with the monoclonal antibody trastuzumab is standard of care in combination with chemotherapy [11]. Adjuvant therapy with trastuzumab for HER2+ breast cancer results in improved recurrence-free survival and lower rate of recurrence within the first 5 years of treatment [12]. Intravenous immunoglobulin has been shown to reduce exposure and increase clearance of therapeutic antibody [13]. Fortunately, our patient has responded well to breast cancer treatment despite the concern of IVIG potentially increasing trastuzumab clearance. Further studies are needed to elucidate the specific interaction between IVIG and trastuzumab. This case highlights a patient with anti-TIF1γ positive dermatomyositis and bilateral breast cancer safely treated with trastuzumab for breast cancer and IVIG for dermatomyositis.

Conclusion

Dermatomyositis is associated with underlying malignancy so prompt workup for cancer should be pursued upon diagnosis. Antibodies against TIF1γ are strongly associated with concomitant cancer in dermatomyositis. We present a patient with anti-TIF1γ positive amyopathic dermatomyositis treated with trastuzumab for associated breast cancer and IVIG for dermatomyositis. If concomitant cancer requires antibody immunotherapy, IVIG may be an appropriate treatment for dermatomyositis without appreciably increasing antibody clearance.

Potential conflicts of interest

The authors declare no conflicts of interest.

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