Anti-transcriptional intermediary factor-1γ antibody-positive dermatomyositis in a patient with triple-negative breast cancer treated with adjuvant capecitabine

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Key words: Anti-transcriptional intermediary factor-1γ; capecitabine; dermatomyositis; triple-negative breast cancer.

INTRODUCTION

Dermatomyositis (DM) is an idiopathic inflammatory myopathy with significant heterogeneity with regards to clinical presentation including variable degrees of myositis and cutaneous findings.[1] Over 40 medications have been implicated in drug-induced inflammatory myopathy.[2] There are 4 case reports of 5-fluorouracil causing DM with 3 patients having metastatic disease.[3-6] Anti-transcriptional intermediary factor-1γ (anti-TIF-1γ) antibody-positive DM is associated with an increased risk of cancer.[1,7,8] While there are case reports of anti-TIF-1γ antibody-positive DM associated with triple-negative breast cancer (TNBC), the incidence has not been well established.[9] We present a unique case of a patient with TNBC treated with neoadjuvant curative-intent chemotherapy and surgery who developed anti-TIF-1γ antibody-positive DM after starting adjuvant capecitabine despite no evidence of active malignancy.

Abbreviations used:

Anti-TIF-1γ:	anti-transcriptional intermediatory factor-1γ
CI:	confidence interval
CPK:	creatine phosphokinase
DM:	dermatomyositis
MMF:	mycophenolate mofetil
TNBC:	triple-negative breast cancer

CASE

A 60-year-old woman diagnosed with clinical stage IIIB TNBC was treated with neoadjuvant doxorubicin and cyclophosphamide followed by paclitaxel. She underwent a left lumpectomy with an axillary sentinel lymph node biopsy revealing residual cancer in the breast. She began adjuvant capecitabine 1250 mg/m^2 twice daily on days 1 to 14 every 3 weeks.[10] One week after beginning the second cycle, she developed pruritic and erythematous raised lesions over her bilateral forearms and right knee, and erythematous papules over her metacarpophalangeal joints without muscle weakness or myalgia. Capecitabine was discontinued and she was referred to dermatology. She started triamcinolone acetonide 0.1% ointment twice daily for a suspected drug-induced lichenoid eruption. She experienced partial improvement in symptoms and resumed capecitabine 1 week later.

Three weeks after resuming capecitabine, the lesions on her hands, consistent with Gottron papules, became more pronounced (Fig 1, *A*). She developed a poikilodermatous eruption of her upper back, consistent with a Shawl sign (Fig 1, *B*), and bilateral palmar nodules. Serologic autoimmune

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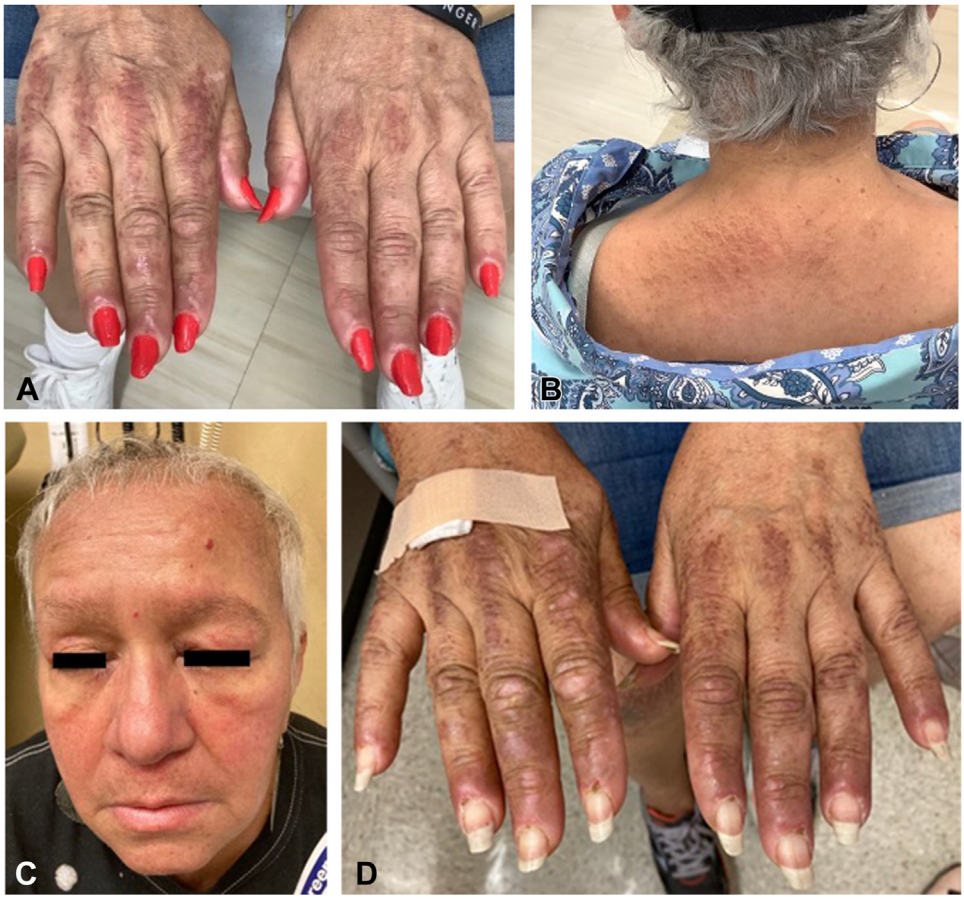

Fig 1. A, Dorsal hand lesions consistent with Gottron papules. **B,** Poikilodermatous eruption of upper back consistent with Shawl sign. **C,** Periorbital erythema consistent with a heliotrope eruption. **D,** Inflammatory changes of figure nail folds.

testing using MyoMarker 3 Plus Profile was moderately positive for anti-TIF-1γ antibodies (Table I). A shave biopsy of her right forearm revealed interface dermatitis (Fig 2). Capecitabine was discontinued after completion of 3 cycles given concern for drug-induced DM.

Her symptoms continued to worsen over the next week. She developed periorbital erythema consistent with a heliotrope eruption (Fig 1, *C*) and inflammatory changes of her fingernail folds (Fig 1, *D*) associated with myalgia. Laboratory findings revealed creatine phosphokinase (CPK) 79 U/L (normal: 25-175 U/L), lactate dehydrogenase 214 U/L (100-220 U/L), erythrocyte sedimentation rate 21 mm/hour (0-24 mm/h), C-reactive protein 5.14 mg/L (<5.1 mg/L), and aldolase 4.9 U/L (3.3-10.3 U/L). She started prednisone 60 mg daily and hydrocortisone 2.5% cream twice daily to her face and continued use of triamcinolone ointment twice daily to her body. She noticed rapid improvement in pruritus and periorbital edema with slower improvement of skin eruptions. Because a drug-induced etiology was high on the differential and the suspected culprit medication, capecitabine, had been discontinued, prednisone was tapered over 4 weeks.

As the prednisone dosage was reduced, her eruption quickly recrudesced. She developed progressive dysphagia to solids then liquids with nasal regurgitation. Laboratory findings noted CPK 2541 U/L, lactate dehydrogenase 262 U/L, erythrocyte sedimentation rate 72 mm/hour, C-reactive protein 45.45 mg/L, and aldolase 13.5 U/L. She was hospitalized for urgent evaluation and treated with intravenous methylprednisolone 1 g daily for 3 days followed by prednisone 60 mg daily with a slow taper to prednisone 20 mg daily, intravenous immunoglobulin 2 g/kg divided over 2 days, and mycophenolate mofetil (MMF) 250 mg twice daily, increased to 750 mg twice daily. CPK slowly down trended and normalized 17 days after initiation of treatment. She was discharged after 1 month. Three

Table I. Myositis panel

Antibody name	Result
Anti-Jo-1	<20*
Anti-PL-7	Negative
Anti-PL-12	Negative
Anti-EJ	Negative
Anti-OJ	Negative
Anti-SRP	Negative
Anti-Mi-2	Negative
Anti-TIF-1γ	73*
Anti-MDA-5	<20*
Anti-NXP-2 (P140)	<20*
Anti-SAE1, IgG	<20*
Anti-PM/Scl-100	<20*
Anti-Ku	Negative
Anti-SS-A 52kD, IgG	<20*
Anti-U1 RNP	<20*
Anti-U2 RNP	Negative
Anti-U3 RNP (Fibrillarin)	Negative

*Negative: <20, weak positive: 20-39, moderate positive: 40-80, and strong positive: >80.

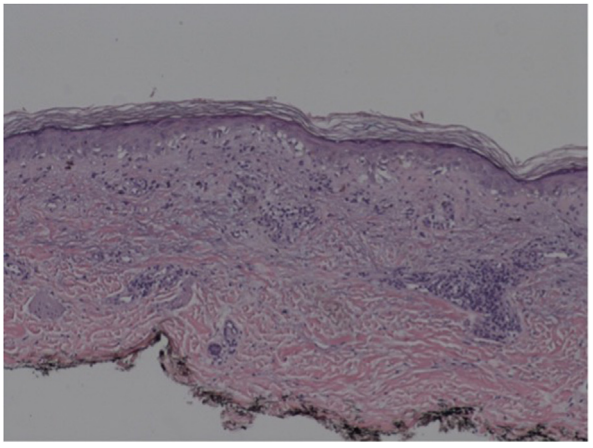

Fig 2. Hematoxylin and Eosin (H&E: medium power) staining of a shave biopsy of the patient's eruption showing interface dermatitis consistent with her diagnosis of dermatomyositis.

months after discharge, prednisone was increased to 30 mg daily due to persistent dysphagia. She remains on MMF 750 mg twice daily with a slow taper of prednisone. Her cutaneous and systemic DM remains quiescent.

DISCUSSION

This is a rare case of a patient with TNBC who presented with anti-TIF-1γ antibody-positive DM after starting treatment with capecitabine. She was initially treated with neoadjuvant chemotherapy followed by surgery with curative intent. At the time of receiving capecitabine, she had no evidence of clinical or radiographic disease. There are 4 case reports of DM associated with oral 5-fluorouracil, including one patient with metastatic cecal adenocarcinoma treated with tegafur[3] and 2 patients, one patient with metastatic breast cancer[4] and another patient with metastatic gastric adenocarcinoma,[5] treated with capecitabine. There is a single case of capecitabine-induced DM without metastatic disease in a patient with gastric cancer who underwent a subtotal gastrectomy.[6]

Anti-TIF-1γ antibodies are strongly associated with malignancy in patients with DM. A meta-analysis of 1962 patients showed a prevalence of cancer-associated DM of 0.41 (95% confidence interval [CI]: 0.36-0.45) among patients with anti-TIF-1γ antibodies with an increased odds ratio of cancer of 9.37 (95% CI: 5.37-16.34).[7] A cohort of 48 patients with anti-TIF-1γ-positive DM revealed 4 patients with breast cancer[8] although the incidence in patients with TNBC is limited to case reports.[9] Patients with anti-TIF-1γ-positive DM have more extensive skin involvement compared to patients with DM with other myositis antibodies, including characteristic findings of palmar hyperkeratotic papules as seen in our patient.[11]

Corticosteroids are the mainstay treatment regardless of suspected drug-induced or paraneoplastic etiology. The recommended dose of oral prednisone is 1 mg/kg/day followed by a slow taper once the DM has become clinically and biologically inactive.[12] Intravenous methylprednisolone therapy can be used for severe DM including extramuscular manifestations.[12] In patients with esophageal impairment, such as our patient, combined high-dose steroids and intravenous immunoglobulin can be used as first-line therapy based on a retrospective study of 73 patients with steroid-refractory polymyositis/DM with esophageal involvement that demonstrated rapid resolution of esophageal dysfunction in over 80% of patients.[13] Immunosuppressive therapy options include azathioprine, methotrexate, cyclosporine, cyclophosphamide, and MMF.[12]

We favor malignancy as the cause of our patient's DM rather than capecitabine. Given the strong association between anti-TIF-1γ antibodies and malignancy, the presence of these antibodies is highly suggestive of a paraneoplastic disease process, which does not necessarily have a temporal relationship with the diagnosis of malignancy.[14] This novel case highlights the importance of recognizing clinical features of DM in patients without active malignancy. Maintaining a high degree of clinical suspicion will lead to prompt diagnosis and treatment.

Conflicts of interest

None disclosed.

REFERENCES

1. Wolstencroft PW, Fiorentino DF. Dermatomyositis clinical and pathological phenotypes associated with myositis-specific autoantibodies. *Curr Rheumatol Rep*. 2018;20(5):28.
2. Dourmishev LA, Dourmishev AL. Activity of certain drugs in inducing of inflammatory myopathies with cutaneous manifestations. *Expert Opin Drug Saf*. 2008;7(4):421-433.
3. Akiyama C, Osada A, Sou K, et al. A case of dermatomyositis triggered by tegafur. *Acta Derm Venereol*. 1997;77:490.
4. Saraswat N, Verma R, Neema S, Kumar S. A case of capecitabine-induced dermatomyositis. *Indian J Pharmacol*. 2018;50(6):350-353.
5. Chen FW, Zhou X, Egbert BM, Swetter SM, Sarin KY. Dermatomyositis associated with capecitabine in the setting of malignancy. *J Am Acad Dermatol*. 2014;70(2):e47-e48.
6. Kawachi Y, Koike Y, Kano T, et al. Paraneoplastic dermatomyositis triggered and exacerbated by oral 5-fluorouracil administration. *Eur J Dermatol*. 2008;18(2):195-196.
7. Best M, Molinari N, Chasset F, Vincent T, Cordel N, Bessis D. Use of anti-transcriptional intermediary factor-1 gamma autoantibody in identifying adult dermatomyositis patients with cancer: a systematic review and meta-analysis. *Acta Derm Venereol*. 2019;99:256-262.
8. Fujimoto M, Hamaguchi Y, Kaji K, et al. Myositis-specific anti-155/140 autoantibodies target transcription intermediary factor 1 family proteins. *Arthritis Rheum*. 2012;64(2):513-522.
9. Kubececk O, Soukup T, Paulik A, Jopecky J. Dermatomyositis with anti-TIF-1γ antibodies as a presenting symptom of underlying triple-negative breast cancer: a case report. *BMC Cancer*. 2016;16:684.
10. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *NEJM*. 2017;376:2147-2159.
11. Fiorentino DF, Kuo K, Chung L, Zaba L, Li S, Casciola-Rosen. Distinctive cutaneous and systemic features associated with antitranscriptional intermediary factor-1γ antibodies in adults with dermatomyositis. *J Am Acad Dermatol*. 2015;72(3):449-455.
12. Marie I, Mouthon L. Therapy of polymyositis and dermatomyositis. *Autoimmun Rev*. 2011;11:6e13.
13. Marie I, Menard JF, Hatron PY, et al. Intravenous immunoglobulins for steroid-refractory esophageal involvement related to polymyositis and dermatomyositis: a series of 73 patients. *Arthritis Care Res*. 2010;62(12):1748-1755.
14. Zampieri S, Valente M, Adami N, et al. Polymyositis, dermatomyositis and malignancy: a further intriguing link. *Autoimmun Rev*. 2010;9(6):449-453.