Rare diagnosis of locally advanced triple-negative breast cancer with paraneoplastic dermatomyositis: A case report and literature review

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Abstract. Paraneoplastic dermatomyositis (DM) is a rare autoimmune condition that primarily affects the skin and muscles; it is associated with various malignancies, including breast cancer. The present case report investigates the clinical presentation, therapeutic considerations and relevant literature regarding DM in the context of locally advanced triple-negative breast cancer (TNBC). A 43-year-old female patient presented with progressive myalgia, dysphagia and characteristic skin rashes. Subsequent investigations confirmed locally advanced TNBC and concomitant DM. Due to the severely weakened state of the patient, the standard treatment of neoadjuvant chemotherapy was contraindicated. The patient initially received corticosteroid therapy, which led to partial symptom improvement, followed by a modified radical mastectomy and adjuvant chemotherapy. Following surgical intervention, the patient experienced significant alleviation of DM symptoms. The present study underscores the critical role of early malignancy identification and intervention in managing DM associated with breast cancer; in addition, it explores the epidemiology, risk factors, pathogenesis, diagnostic modalities and treatment strategies for breast cancer-associated DM. The potential challenges in treatment selection are highlighted, particularly in patients with severe presentations. Mastectomy can emerge as a viable therapeutic option to achieve symptom control and facilitate subsequent oncological management.

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Introduction

Breast cancer is one of the malignancies that is occasionally associated with paraneoplastic dermatomyositis (DM) (1). Triple-negative breast cancer (TNBC) is a type of breast cancer that lacks expression of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), and accounts for 10-24% of all breast cancer cases (1). Locally advanced breast cancer (LABC) is rare and defined as patients with stage III breast cancer according to the system defined by the American Joint Committee on Cancer, the 7th edition. Biologically aggressive phenotypes of LABC include inflammatory breast cancer and other types of rapidly proliferating breast cancer, such as TNBC (2). Neoadjuvant chemotherapy is the standard treatment for locally advanced TNBC and has been shown to notably improve patient outcomes (3).

DM is a debilitating autoimmune disease that primarily affects muscle tissue and skin. It exhibits several characteristic symptoms, including progressive muscle weakness, which is particularly evident in proximal muscles such as the shoulders and buttocks. Patients often present with distinctive rashes, including heliotrope (purple discoloration on the eyelids) and Gottron's papules (raised, scaly papules on the knuckles) (4). The precise etiology of DM remains elusive; however, it is classified as an autoimmune disease in which the immune system targets healthy tissue (5).

Paraneoplastic syndrome has been observed to link seemingly disparate conditions, such as DM, to occult cancer. These syndromes arise when a tumor prompts the immune system to generate aberrant antibodies or other immune responses that affect distant organs (6). The main symptoms include progressive proximal muscle weakness, extra-muscular manifestations such as dyspnea or dysphagia, and skin changes (7). Although oncological treatments can provide significant relief from DM, it is not clear whether the severity of DM is associated with the severity of the tumors. Furthermore, there are no standard treatment protocols regarding DM combined with breast cancer (8).

It is estimated that 15-30% of adult DM cases are paraneoplastic DM, with breast cancer being the primary factor (9,10). Despite its relatively low incidence, early diagnosis and

management of DM are crucial to improving patient prognosis. As symptoms of DM can occur before, during and even after the onset of breast cancer, it is challenging to recognize the potential link between the two diseases (11). The present study aimed to report the management of a case of locally advanced TNBC with DM (Fig. 1) that achieved significant remission while reviewing the literature to elucidate the current understanding of this paraneoplastic syndrome, and to explore its pathogenesis, clinical manifestations, diagnosis and treatment strategies.

Case report

Clinical findings. In August 2023, a 43-year-old woman with no history of underlying medical or genetic conditions presented to the emergency department of Peking Union Medical College Hospital (Beijing, China) with a 1-month history of progressive limb weakness, dysphagia and a 1-week history of dyspnea. The patient presented with recurrent purplish facial erythema, marked edema with pruritus, and recent progression involving the trunk and limbs, with suspected involvement of the muscles used for swallowing. The preliminary diagnosis from the dermatologist was DM. Due to the potential association with carcinoma, the dermatologist recommended further comprehensive examination.

A physical examination revealed an irregular mass that was ~5.5 cm from the nipple in the right breast, with a hard texture, unclear boundary and poor mobility. Upon initial evaluation, the manual muscle test score was recorded as 4/5 in proximal muscles, and symmetrical sensation was observed (12). Muscle tone and limb strength were normal on second examination. Physiological reflexes were present, and no pathological reflexes were elicited. Doppler ultrasound demonstrated a low echogenic and irregular mass in the right breast, with weak echogenic deposition behind and a rich blood flow signal within the mass (Fig. 2A). Ultrasound also revealed multiple lymph nodes in the right axilla. Mammography showed a dense mass in the right breast with irregular margins and indistinct borders, and traces of calcification within the mass (Fig. 2B). The mass was classified as category 4c using the breast imaging reporting and data system standards (13).

Laboratory tests indicated that the complete blood count was close to normal, while blood biochemistry revealed the following: Alanine transaminase, 29 U/l (normal range, 0-40 U/l); lactate dehydrogenase level of 256 U/l (normal range, 109-245 U/l); creatinine, 41 μmol/l (normal range for adults, 44-97 μmol/l); urea, 2.00 mmol/l (normal range, 3.2-7.1 mmol/l); creatine kinase (CK), 1,010 U/l (normal range, 18-198 U/l); CK-MB-mass, 9.9 μg/l (normal range, 0-5 μg/l); myoglobin, 252 μg/l (normal range, 0-90 ng/ml); and high-sensitivity C-reactive protein, 4 mg/l (normal range, 0.068-8.2 mg/l). The coagulation profile demonstrated a fibrinogen level of 4.24 g/l (normal range, 2-4 g/l), a D-dimer concentration of 2.38 mg/l (normal range, 0-5 mg/l). Additionally, the rheumatoid factor, anti-streptococcal hemolysin 'O' test, antinuclear antibody profile, immunoglobulin and complement levels were all revealed to be clinically negative, and so were the tumor markers. Cardiac ultrasound suggested that the left ventricular ejection fraction was 66%, and there were no obvious abnormalities in the intracardiac structure and blood flow. A blood sample was sent to the laboratory (KingMed Diagnostics Group Co., Ltd.), where the antibody spectrum of myocarditis was assessed using a commercially available kit (KingMed Diagnostics Group Co., Ltd.), to investigate the potential paraneoplastic nature of DM. Testing revealed that anti-transcription intermediary factor 1-γ autoantibodies were positive, providing evidence for the association of DM with malignancy. Other antibodies of the myocarditis spectrum (including ribonucleoprotein, anti-Ku, anti-PM-Scl, anti-Jo-1, anti-transcription intermediary factor 1-γ, and anti-PL-7 antibodies, etc.) were tested but found to be negative, ruling out other possible subtypes of DM linked to these antibodies. Electromyography suggested myogenic damage to the upper and lower extremities (Fig. 2C and D), and a CT scan of the chest, abdomen and pelvis suggested that there were no specific abnormalities except for mild subcutaneous soft tissue edema of the chest wall.

Diagnostic assessment. Invasive breast cancer was diagnosed by pathology from a core needle biopsy of the breast in August, 2023, two months after the patient first discovered the lump and 18 days prior to her emergency department visit for suspected DM. TNBC was classified based on the biopsy pathology report of negative expression of ER, PR and HER2 (score 1+) by immunohistochemistry (according to the system defined by the American Joint Committee on Cancer, the 7th edition) (data not shown). The presence of distant metastases to internal organs or bone was ruled out by positron emission tomography-computed tomography examination (Fig. 2E and F) and emission computed tomography of the bones. Consequently, the patient was diagnosed with locally advanced TNBC. According to the medical history of the patient, tumor-related DM was diagnosed by an oncologist and dermatologist.

Treatment. The patient underwent a preliminary multidisciplinary assessment in the emergency department, which included anesthesiology, medical oncology, breast surgery and dermatology. General anesthesia of the patient was not appropriate for surgical treatment due to progressive muscle weakness and the high risk of respiratory distress, and inability to extubate after anesthesia. Neoadjuvant chemotherapy was also not feasible due to the poor general condition of the patient and high risk of chemotherapy side effects.

Outpatient phase. Initial treatment began in September 2023, with methylprednisolone sodium succinate prescribed at 40 mg/day (intravenous infusion). Despite 1 week of therapy, the symptoms of the patient, including limb weakness and dyspnea, were not sufficiently controlled.

Inpatient phase (high-dose corticosteroid pulse therapy). To rapidly alleviate the paraneoplastic syndrome, which was mainly characterized by severe dyspnea and muscle weakness, the patient was admitted to the Department of Dermatology (Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China) in September 2023 and received high-dose corticosteroid pulse therapy (defined as the use of high doses of corticosteroids over a short period to achieve rapid control of symptoms). Upon admission, the treatment regimen was escalated to a prednisone-equivalent dose of 60 mg/day, consisting

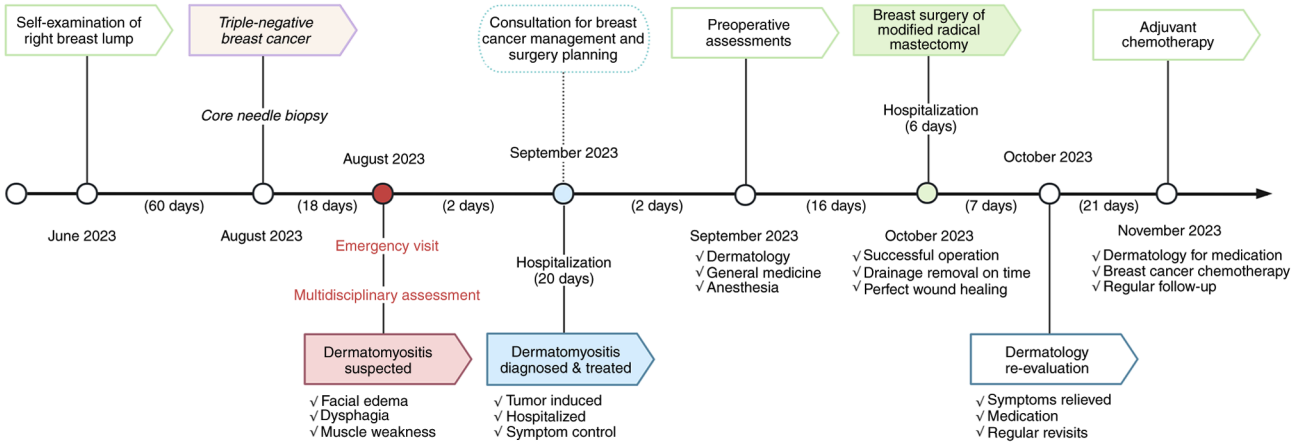

Figure 1. Timeline of the clinical management of this case.

of methylprednisolone 40 mg daily (intravenous infusion) and an additional 8 mg oral methylprednisolone daily, aiming to achieve rapid symptom control. Corticosteroid therapy was initiated to rapidly alleviate the symptoms of paraneoplastic DM, including dyspnea and limb weakness. The treatment aimed to stabilize the condition of the patient prior to surgical intervention and improve quality of life. Meanwhile a multidisciplinary consultation was held to assess the condition of the patient and determine timely surgical conditions. Following corticosteroid therapy, the patient demonstrated partial clinical improvement with dyspnea, muscle weakness and cutaneous lesions. Laboratory tests showed a decline in CK levels (40 U/l; normal range, 18-198 U/l), confirming the effectiveness of the treatment. After 4 weeks of adequate corticosteroid treatment, dose tapering was initiated and the preparations for surgery continued as planned.

In October 2023, the patient was admitted to the Department of Breast Surgery (Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China), and a modified radical mastectomy was performed after consultive preparation and joint management by the oncology, dermatology, general medicine and anesthesia departments. During this perioperative period, the patient received intravenous immunoglobulin therapy (human immunoglobulin) at a daily dose of 30 g via intravenous infusion for a total of 5 days. This therapy was initiated to manage DM-related symptoms and to ensure the patient was in optimal condition for the planned surgical procedure. The procedure went well, and TNBC was confirmed (Fig. 2G), with pathological analysis of paraffin-embedded tissue reporting invasive carcinoma of the right breast (non-specific, moderately poorly differentiated, histological grade 3 (American Joint Committee on Cancer, the 7th edition). The tumor was 5x1 cm with multiple intratumorally emboli, no significant nerve invasion and a small amount of intermediate-grade ductal carcinoma seen in the periphery. Mammary adenopathy and fibroadenoma were also observed. No lesions were observed in the nipple and areola, and lymph node metastatic carcinoma was revealed (right axilla 7/12). Immunohistochemical analysis (14) results of the final pathology report were as follows: ER (-), PR (-), androgen receptor (-), HER2 (score 0), Ki-67 proliferation index (80%), p53 tumor suppressor protein (-), CD10 (-), cytokeratin 14 (partial +), cytokeratin 5/6 (-), epidermal growth factor receptor (-), p63 (-), E-cadherin (-) and p120 (-) (data not shown).

On the second postoperative day, the orbital edema, hoarseness, dyspnea and limb weakness of the patient were markedly reduced, and the erythema subsided. The patient recovered from surgery without adverse incidents. A total of 3 weeks after surgery, the patient was able to walk independently, and most of the skin symptoms were relieved, particularly the facial rashes (Fig. 2H and I). A total of 4 weeks after the operation, the patient gained a full recovery and started postoperative adjuvant chemotherapy as scheduled. The patient was administered chemotherapy of epirubicin (150 mg) and cyclophosphamide (900 mg) in a 2-week regimen four times, followed by a docetaxel regimen (150 mg) in a 3-week regimen four times.

The patient is under a regular follow-up of every 6 months, and at the latest checkup in November 2024 was in good general condition, with muscle strength grade score of 5/5, skin rash improved from the previous state, no dysphagia, and no local recurrence or distant metastasis.

Literature review

Epidemiology and risk factors of breast cancer-induced DM. Breast cancer is a well-documented risk factor for DM, a debilitating autoimmune myopathy. Notably, for DM and breast cancer, the risk appears to be bidirectional. Patients with DM have a higher risk of developing cancer, particularly breast cancer, within 5 years of diagnosis (15). This highlights the importance of thorough cancer screening in patients with new-onset DM.

While the exact reasons behind breast cancer specifically triggering DM are yet to be fully elucidated, some potential risk factors are emerging. Research suggests a possible link with specific breast cancer subtypes, particularly aggressive tumors such as TNBC. Additionally, age might play a role, with some studies suggesting a higher prevalence of breast cancer-induced DM in younger women compared with the typical demographic for both conditions. The average age of breast cancer patients with DM is reported to be ~45 years, which is younger than the typical age for breast cancer and

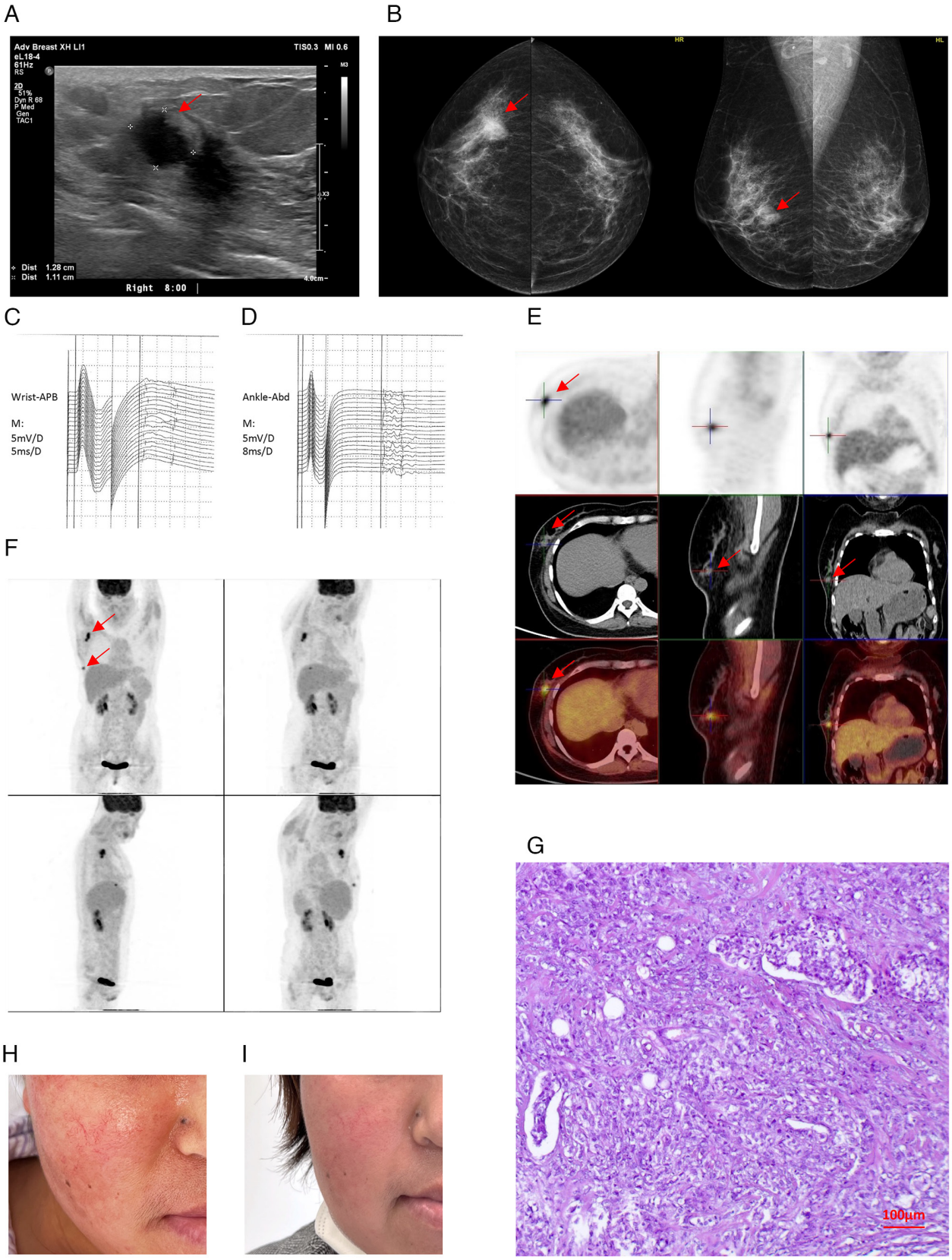

Figure 2. Clinical imaging and pathological findings of triple-negative breast cancer presenting with dermatomyositis. (A) Ultrasound imaging of the breast mass. The mass appears as a well-defined, hypoechoic lesion with irregular margins (red arrow indicating the mass). (B) Mammogram of the breast mass. The mass appears as a dense, spiculated lesion (red arrow indicating the mass). (C) Upper extremity EMG waveform. Denervation potentials are present, indicative of muscle involvement. (D) Lower extremity EMG waveform. Denervation potentials are present, indicative of muscle involvement. (E) Whole-body PET-CT scan results. The mass demonstrates increased fluorodeoxyglucose uptake, indicative of malignancy (red arrow indicating the mass). (F) Whole-body PET-CT axial scans. The mass exhibits intense fluorodeoxyglucose uptake (arrow), consistent with the pathological result. (G) Hematoxylin and eosin staining of the tumor (magnification, x100). (H) Preoperative facial rash and edema. The patient exhibited erythema, swelling and heliotrope rash characteristic of dermatomyositis. (I) Postoperative facial appearance. The rash and edema resolved following tumor resection. EMG, electromyography; PET-CT, positron emission tomography-computed tomography; APB, Abductor Pollicis Brevis muscle activity; ABD, abduction muscle activity.

DM (16). Further research is required to confirm these associations, and to identify additional risk factors for targeted diagnosis and management.

Association between breast cancer and DM: Unveiling pathogenic mechanisms. The precise mechanisms by which breast cancer triggers DM remain elusive. Current hypotheses suggest a complex interplay between the immune system and the tumor microenvironment. A potential explanation involves a phenomenon known as molecular mimicry. Breast cancer cells may express antigens structurally similar to those found in healthy muscle and skin tissues. This resemblance may misdirect cytotoxic T lymphocytes and autoantibody production, targeting healthy tissues and causing DM symptoms (17).

Another compelling theory suggests a role for anti-melanoma differentiation-associated gene 5 (anti-MDA5) autoantibodies. These antibodies, often elevated in patients with DM, have been linked to specific oncological conditions, including breast cancer (18). Their presence might contribute to tissue damage through various pathways, including disruption of cellular protein synthesis and induction of inflammatory responses (19).

A previous study suggested a potential role for the tumor microenvironment itself in promoting DM. Breast cancer cells may release cytokines and other inflammatory mediators that activate autoreactive immune cells, further contributing to the autoimmune attack on healthy tissues (20). Elucidating the specific contribution of these factors and their interactions is crucial for developing targeted therapeutic strategies for this paraneoplastic syndrome. Ongoing research in this area explores the role of specific immune cell subsets, cytokine profiles and the identification of novel autoantibodies associated with breast cancer-induced DM (21). Investigating these intricate mechanisms may hold promise to not only improve diagnosis but also develop potential novel immunomodulatory therapies.

Challenges and tools in diagnosing breast cancer-associated DM. DM is characterized by distinctive clinical features. Proximal muscle weakness, predominantly affecting the shoulders, hips and thighs, is a hallmark symptom. Patients often have trouble climbing stairs, rising from a seated position or raising their arms overhead. Additionally, characteristic rashes can offer valuable diagnostic clues. The heliotrope rash, a violaceous discoloration on the eyelids, and Gottron's papules, raised, scaly bumps on the knuckles and extensor surfaces of the knees and elbows, are frequently observed (22).

However, diagnosing breast cancer-induced DM presents a unique challenge. The timing of the two conditions can vary. DM can manifest before, concurrently with, or even years after the diagnosis of breast cancer (23). This variability requires heightened awareness and a multi-pronged diagnostic approach.

Diagnosis relies on clinical evaluation, including a detailed history and examination of muscle weakness and characteristic rashes. Laboratory investigations often reveal elevated muscle enzymes such as CK. Skin biopsies from affected areas can demonstrate specific histological features supportive of DM. Additionally, the presence of specific autoantibodies, such as anti-MDA5 autoantibodies, can strengthen the diagnosis and potentially link it to an underlying malignancy (18). While these tools offer valuable insights, further research is needed to identify more specific biomarkers for a definitive diagnosis of breast cancer-induced DM, particularly in cases with atypical presentations.

Managing DM and eradicating breast cancer using a two-pronged approach. The management of breast cancer-induced DM necessitates a dual therapeutic strategy. First, addressing the underlying inflammatory processes driving DM is crucial. Corticosteroids, particularly prednisone, are the primary treatment, and they suppress the immune system and reduce muscle inflammation and weakness (24). In severe cases or those unresponsive to corticosteroids alone, immunosuppressant medications such as azathioprine, methotrexate or mycophenolate mofetil can be used in conjunction to achieve optimal disease control (25).

Concurrently, effective treatment of the underlying breast cancer is paramount for sustained improvement in DM symptoms. Breast cancer treatment depends on tumor stage, hormone receptor status and HER2 expression. Surgery remains a cornerstone of treatment, with the extent ranging from lumpectomy for early-stage tumors to mastectomy for more advanced presentations (26). Adjuvant therapy with chemotherapy and/or radiation therapy may be recommended based on individual risk factors and tumor characteristics.

Previous research has highlighted the potential benefits of early and aggressive breast cancer treatment in improving DM outcomes. Prompt diagnosis and initiation of appropriate therapy for the malignancy can significantly reduce disease activity and improve muscle strength in patients with DM (11). This emphasizes the importance of a collaborative approach between rheumatologists and oncologists to ensure optimal management of both conditions.

Prognostic considerations and management landscape. The prognosis for patients with breast cancer-induced DM depends on two crucial factors: Early diagnosis and successful treatment of the underlying malignancy. Prompt identification and aggressive breast cancer management markedly improve DM outcomes. Early intervention with appropriate breast cancer therapy has been shown to lead to a marked reduction in DM disease activity and a notable improvement in muscle strength (27). This highlights the need for heightened awareness of DM in patients with breast cancer, especially those with unexplained muscle weakness or characteristic rashes.

Discussion

LABC is a subset of breast cancer that is characterized by advanced breast tumors in the absence of distant metastasis. The definition of LABC encompasses tumors >5 cm in size with regional lymphadenopathy (N1-3), as well as tumors of any size with direct extension to the chest wall or skin (including ulcer or satellite nodules). Patients with LABC generally have a poor prognosis, with a high risk of local recurrence and distant metastasis. LABC is currently estimated to account for 10% of breast cancer cases in women (28). It can be classified as an operable or inoperable disease, depending on the stage of

the tumor (T4, N2 or N3). Historically, the preferred treatment option for inoperable LABC was neoadjuvant chemotherapy; however, in selected patients with limited local disease (axillary lymph node metastases, but not fixed, moderate skin involvement), radical mastectomy may be considered as the primary treatment option.

For women with locally advanced TNBC, neoadjuvant chemotherapy is a viable systemic treatment. It has been demonstrated to induce pathological complete remission, increase surgical success, and reduce the extent of surgical intervention, thereby minimizing surgical morbidity. A number of clinical studies have demonstrated that 30-40% of patients achieve a complete clinical response, while 50-60% achieve a partial response (29). Following the completion of neoadjuvant chemotherapy, patients may proceed with definitive local therapy (30). The objective of surgical intervention is the complete excision of the primary tumor, including any loco-regional disease and involved skin or muscles. It is recommended that patients who have undergone surgery receive postoperative radiation therapy to minimize the risk of local recurrence (31).

Breast cancer in the context of DM is a rare and complex disease. The primary symptoms of DM manifest primarily as dermatological and musculoskeletal conditions, with the potential to evolve into more severe presentations, such as severe dyspnea. The patient in the present study presented with this condition. The association between breast cancer and DM has been confirmed through epidemiological studies (3); however, the precise mechanism remains unclear. When a tumor complicates DM, excision of the tumor lesion is a more effective treatment to alleviate the symptoms of DM compared to conventional treatments, such as immunosuppressive therapies or corticosteroids (32,33). The treatment of DM is primarily based on systemic corticosteroids (34).

The notable improvement of DM symptoms following tumor resection in the current case may provide insights into the pathophysiological links between the two conditions. A potential explanation is that tumor antigens, which may share structural similarity with autoantigens in muscle and skin tissues, are eliminated, thereby halting the autoimmune response (35). Another possibility is the cessation of autoantibody production that had been stimulated by the presence of the tumor (36). Additionally, tumors may secrete factors that modulate the immune response, exacerbating autoimmune symptoms, which subside once the tumor is removed (37). While these mechanisms remain hypothetical, they highlight the importance of tumor removal as a potential therapeutic strategy for paraneoplastic syndromes. Future research should focus on elucidating these complex interactions to develop targeted treatments.

There is no standardized treatment for breast cancer associated with DM, and individualized treatments must be based on the condition of the patient. For refractory LABC with DM, the timing of treatment for DM and breast cancer is also crucial. Dias *et al* (11) reported that severe muscle symptoms should be controlled with steroids before radical excision of breast cancer. However, not all steroid treatments can achieve DM remission. In the present case, potential risks associated with corticosteroid use, such as delayed wound healing and surgical site infections, were carefully managed through close monitoring of the condition of the patient. Additionally, topical treatments, including Elosone and boric acid wet compresses, were employed to control skin lesions effectively. No antibiotics were required, as no signs of infection were observed throughout the treatment.

Furthermore, in the present study, the administration of steroids prior to surgical intervention resulted in a longer overall period of disease control. The patient exhibited only a negligible response to steroid treatment, concomitant with a substantial and unremitting deterioration in their general condition (severe and persistent dyspnea). In light of this critical condition, both surgical intervention and chemotherapy were deemed to be highly risky for the patient. Following a comprehensive risk assessment and thorough communication between the patient and their physician, a mastectomy was performed, and the patient made a full recovery. This case may be indicative of DM as a paraneoplastic syndrome manifestation. A limitation of this study is the short follow-up period (latest follow-up was 18 months post-surgery). The results of therapy and any changes to the health of the patient will continue to be monitored.

In conclusion, in adult patients presenting with DM, doctors must prioritize cancer screening to ensure timely diagnosis of potential malignancies, and the necessity for multidisciplinary collaboration in the management of the condition of the patient. When patients present with relatively severe paraneoplastic muscle symptoms, the upfront resection of the tumor may provide rapid relief of symptoms, thereby allowing the subsequent treatment to be initiated, which could improve the prognosis of the patient.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YS contributed to data collection and manuscript writing. YX and XH contributed to data acquisition and interpretation. QS and YL supervised the study, designed the study and critically revised the manuscript. YS, YX, QS and YL confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the Declaration of Helsinki and its later amendments.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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