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Case Report

Anti-EJ antibody-positive interstitial pneumonia with breast cancer improved by combining immunosuppressive therapy and chemotherapy

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ABSTRACT

We present a case of a 45-year-old woman diagnosed with interstitial pneumonia (IP) during a comprehensive breast cancer evaluation. Although the patient showed no obvious clinical symptoms of polymyositis or dermatomyositis, the presence of anti-glycyl-transfer ribonucleic acid synthetase antibodies confirmed anti-synthetase syndrome. The patient began methylprednisolone for treatment of the IP. She then received preoperative chemotherapy with epirubicin and cyclophosphamide before undergoing a mastectomy. A significant improvement was seen in the patient's IP during treatment. This case emphasizes the potential advantages of personalized immunosuppressive therapy for patients who are simultaneously diagnosed with anti-synthetase syndrome and cancer.

1. Introduction

Anti-aminoacyl tRNA synthetase (anti-ARS) autoantibodies, which include anti-glycyl-transfer ribonucleic acid synthetase (anti-EJ) antibodies, are recognized as myositis-specific auto-antibodies. Patients presenting with a combination of anti-ARS antibodies and clinical manifestations, such as interstitial pneumonia (IP), fever, arthritis, Raynaud's phenomenon, or mechanic's hands, are diagnosed as anti-synthetase syndrome (ASSD) [1].

In the present case, IP was detected subsequent to a breast cancer diagnosis, with further evaluation revealing positive anti-EJ antibodies. Although malignancies are common among patients with dermatomyositis [2], reduced incidence of malignancies has been observed in patients with both IP and dermatomyositis [3]. Despite documented cases of patients with coexisting ASSD, IP, and breast cancer [4,5], standardized treatment guidelines for those with IP in conjunction with malignancy have yet to be established. This report outlines the treatment of a patient with breast cancer and anti-EJ antibody-positive IP, and reports a favorable treatment outcome.

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2. Case presentation

A 45-year-old woman presented with swelling and erythema of her right breast and was diagnosed with invasive ductal carcinoma of the breast (estrogen receptor, 40 %, progesterone receptor, 0 %, human epidermal receptor 2-negative, and MIB-1 index, 42 %) by core needle biopsy. Magnetic resonance imaging (MRI) revealed a 7-cm tumor in the right inner quadrant with potential extensive skin involvement (Fig. 1). The clinical stage was determined as T4cN0M0 Stage IIIB.

IP was incidentally detected on chest computed tomography (CT), prompting a referral to the respiratory department. Chest CT showed a predominant, basal, ground-glass opacity with a reticular pattern, consistent with nonspecific interstitial pneumonia (NSIP) pattern (Fig. 2A). Elevated serum levels of IP markers, Krebs von den Lungen-6 (KL-6) (2903 U/mL) and surfactant protein-D (SP-D) (731 ng/mL), were observed (Table 1). Blood tests related to IP indicated the presence of anti-EJ antibodies, while other antibodies associated with ARS, anti-histidyl (Jo-1), threonyl (PL-7), alanyl (PL-12), isoleucyl tRNA synthetase antibodies, anti-Mi-2, anti-Ku, PM-scl100, and PM-scl75, were negative. Physical examination revealed sclerosis of the patient's fingers and an eruption of the right knee. However, skin biopsy did not lead to a diagnosis of dermatomyositis. Slight creatine kinase (165 U/L) and aldolase (7.7U/L) elevations were noted (normal ranges are 41–153 U/L and 2.1–6.1 U/L, respectively); however, there was no diminished muscle strength, and

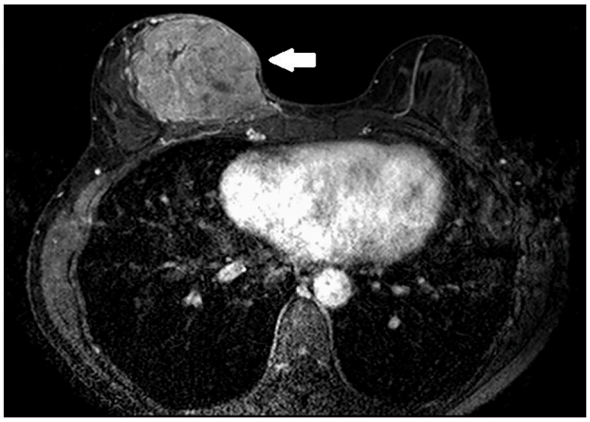

Fig. 1. Magnetic resonance imaging of breast cancer before treatment. The tumor was roughly 7 cm in diameter and in contact with the chest wall.

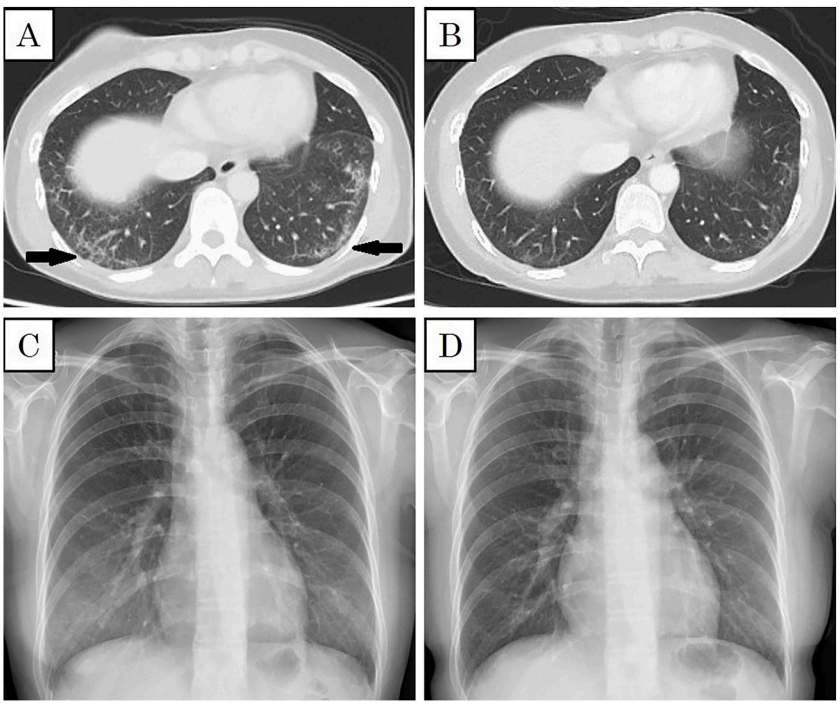

Fig. 2. The initial computed tomography image (A) showed a ground glass opacity and reticular shadows in bilateral lower lobes, and a subpleural spared area was observed. Computed tomography findings improved before surgery (B). Chest X-ray examination immediately before operation (C) and at 3 months (D).

Table 1
Blood analysis.

	Result	Unit		Result	Unit
WBC	3900	/μL	AST	15	U/L
Neut	68.2	%	ALT	15	U/L
RBC	468×10^4	/μL	Cre	0.46	mg/dL
Hb	14.4	g/dL	CK	168	U/L
Plt	30.5×10^4	/μL	ALD	7.7	U/L
CRP	0.03	mg/dL	KL-6	2903	U/L
LDH	272	U/L	SP-D	731	ng/mL

WBC: white blood cell count, Neut: neutrophil, Hb: hemoglobin, Plt: platelet count, CRP: C-reactive protein, LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Cre: creatinine, CK: creatine kinase, ALD: aldolase, KL-6: Krebs von den Lungen-6, SP-D: Surfactant Protein-D.

full-body MRI showed no abnormal signals associated with myositis. Consequently, the patient was diagnosed with ASSD, based on Connors' criteria, but failing to meet Bohan and Peter criteria for dermatomyositis.

Pulmonary function tests showed restrictive impairment and reduced diffusion capacity: vital capacity of 2.36 L (77.6 % of the predicted value), forced expiratory volume of 2.02 L in 1 sec (82.5 % of the predicted value), and lung diffusing capacity for carbon monoxide of 9.57 mL/min/mmHg (52.6 % of the predicted value). During a 6-min walking test, oxygen desaturation was observed, with the lowest recorded percutaneous oxygen saturation at 91 %. Due to these findings and the patient's symptomatic dyspnea on exertion, treatment with 20 mg of methylprednisolone was initiated for IP. On the fifth day post-initiation, the patient began her first cycle of neoadjuvant chemotherapy for breast cancer with epirubicin and cyclophosphamide (EC; epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2). Within two weeks, there was a marked improvement in her respiratory symptoms and a decline in the serum concentration of SP-D. After one month, chest CT images indicated improvement in regard to ground-glass opacities, prompting a reduction of methylprednisolone to 16 mg/day. The dose of methylprednisolone was reduced by 4 mg/day every 3 weeks. Following reduction of the tumor to 5.0 cm after four cycles of EC and improved IP imaging (Fig. 2B), surgical intervention for breast cancer was conducted while the patient was on 4 mg of methylprednisolone. The surgery proceeded without IP exacerbation or other respiratory complications (Fig. 2C and D). Histopathological examination of the resected specimen revealed microscopic metastasis in the right axillary lymph node, but no malignant tissue in the skin margin. One-month after surgery, serum levels of KL-6 had decreased to 574 U/mL and anti-ARS antibodies were undetectable, leading to cessation of methylprednisolone. Subsequent adjuvant chemotherapy with paclitaxel was administered, and no IP exacerbations have been reported for more than one year.

3. Discussion

Cytoplasmic aminoacyl-tRNA synthetases facilitate amino acid binding to specific tRNA molecules. Anti-EJ antibodies are among the eight antibodies detected against amino acids [1]. Anti-EJ antibodies were positive for 1–7% of anti-ARS antibodies [6–8]. Both Solomon's and Connors' criteria are employed to diagnose ASSD. This patient met Connors' criteria, but not Solomon's, due to lack of clinical features other than IP. Connors' criteria, widely accepted for defining ASSD, remain practical. However, this method is expert-opinion-based and unvalidated, and its performance remains unassessed [9]. Some studies regard Solomon's criteria as the gold standard [10]. Patients with anti-ARS antibodies may develop myositis and skin symptoms later, necessitating vigilant monitoring.

This report highlights a unique case of anti-EJ antibody-positive ASSD coexisting with IP and cancer. ASSD is frequently associated with IP [7]. Malignancy rates are lower in ASSD patients (9 %) compared to dermatomyositis (DM) patients (20–30 %) [11]. Only three reports of malignancies with anti-EJ antibodies exist. These involved retroperitoneal sarcoma, rectal cancer, and nasopharyngeal cancer [12–14]. This reduced malignancy frequency in ASSD may correlate with IP presence, possibly reducing malignancy risk in DM patients [15]. Though the exact mechanism has not been identified, immune activity of anti-ARS antibodies may suppress cancer development [3].

When encountering concurrent autoantibodies and malignancy, paraneoplastic syndromes should be considered. In the present case, the decline in anti-ARS antibody levels post-surgery suggested ASSD as a feature of breast cancer-associated paraneoplastic syndromes. Symptoms of paraneoplastic syndrome typically improve following tumor treatment; however, residual symptoms post-treatment occur [16,17]. Thus, individualized treatments tailored to disease status are vital. In this case, we initiated treatment for IP, considering the patient's symptoms. Aggressive immunosuppressive treatment benefits anti-ARS antibody-associated IP. Typically, IP with anti-EJ antibodies displays an NSIP pattern and responds favorably to corticosteroids [18,19]. Some patients experience recurrence after cessation of corticosteroids [18]; therefore, careful follow-up should be maintained.

EC is a standard regimen for breast cancer. Since cyclophosphamide is sometimes used for IP treatment in concert with corticosteroids [18], it can serve dual purposes: addressing breast cancer and managing IP effectively. However, there is documentation of ASSD exacerbation following docetaxel, cyclophosphamide, and trastuzumab treatment [4], along with EC therapy-induced IP [20,21]. Efficacy and safety of chemotherapy regimens like cyclophosphamide for patients with coexisting malignancies and IP warrant further exploration.

Complication of IP exacerbation after surgery poses challenges in oncological care. Approximately 4.0 % of IP patients experience acute, post-surgical exacerbations (AEs) [22]. While idiopathic pulmonary fibrosis (IPF) is known for postoperative AEs, some studies

have suggested no significant discrepancy of AEs between NSIP and IPF [23]. Thus, caution regarding IP exacerbation in non-IPF patients is imperative. Japanese guidelines for IPF do not recommend corticosteroid use for postoperative AE prevention, but there is limited knowledge regarding preoperative IP management in non-IPF cases. In our view, preoperative IP management, including corticosteroids and cyclophosphamide, enhanced management of AEs in the present case.

4. Conclusions

This study highlights a case of a patient diagnosed with IP and breast cancer who demonstrated a favorable response following treatment with corticosteroids and EC therapy. IP can pose challenges during cancer treatment, especially in a neoadjuvant setting. Nonetheless, chemotherapy regimens that include cyclophosphamide may offer an effective approach to simultaneously manage both cancer and IP.

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Declaration of competing interest

No conflict of interest.

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