Occult breast cancer showing a marked response to pembrolizumab plus gemcitabine and carboplatin therapy complicated by immune-related colitis: A case report

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Abstract. Occult breast cancer (OBC) is a rare condition presenting with axillary or distant lymph node metastases without a detectable primary tumor. Immune checkpoint inhibitors (ICIs) show promise in triple-negative breast cancer (TNBC) treatment; however, their efficacy in OBC remains unclear. The present study describes the case of a 71-year-old woman who presented with left cervical and axillary lymphadenopathy. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (CT) and breast ultrasonography revealed no detectable primary breast lesion. Core needle biopsy of the axillary lymph node confirmed the diagnosis of TNBC (estrogen receptor, 0%; progesterone receptor, 0%; human epidermal growth factor receptor 2 score, 0). The programmed death-ligand 1 combined positive score was >10. Since the patient had stage IV disease with the biological subtype defined by lymph node biopsy, breast magnetic resonance imaging was not performed to avoid delaying systemic therapy. Pembrolizumab (Pembro) combined with gemcitabine and carboplatin was initiated. However, the patient developed a Grade 1 rash after the first cycle and diarrhea after the second cycle, followed by immune-related colitis requiring hospitalization. Notably, the emergence of immune-related adverse events (irAEs) paralleled a marked treatment response, with non-contrast CT after three cycles showing complete resolution of left axillary lymph node metastases. Pembro was discontinued, and the patient has maintained a complete response on eribulin monotherapy for >1 year. The present case suggests an association between irAEs and the clinical effectiveness of ICIs, highlighting the potential of Pembro-containing chemotherapy for OBC treatment, and emphasizing the importance of prompt irAE recognition and management. Lymph node-dominant disease may represent a particularly immunogenic context for ICI therapy.

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Abbreviations: ICI, immune checkpoint inhibitor; TNBC, triple-negative breast cancer; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; Pembro, pembolizumab; irAE, immune-related adverse event; TMB, tumor mutational burden; OBC, occult breast cancer; GEM, gemcitabine; CBDCA, carboplatin; CT, computed tomography; FDG, ^{18}F-fluorodeoxyglucose; CUP, carcinoma of unknown primary site; IHC, immunohistochemistry; GCDFP-15, gross cystic disease fluid protein-15; MRI, magnetic resonance imaging; LVFX, levofloxacin; CD, *Clostridioides difficile*; OS, overall survival

Key words: OBC, TNBC, Pembro, irAE colitis, complete response

Introduction

Immune checkpoint inhibitors (ICIs) have emerged as a promising therapeutic modality for patients with triple-negative breast cancer (TNBC), a subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) expression and associated with an aggressive clinical course and limited treatment options. TNBC accounts for approximately 15-20% of all breast cancers worldwide and is associated with a higher risk of early recurrence and poorer overall survival compared with other subtypes (1,2). The introduction of ICIs has partially improved outcomes in this population, particularly following the KEYNOTE-355 trial, which established pembrolizumab (Pembro) combined with chemotherapy as a standard treatment option for advanced or recurrent TNBC (3). Despite their clinical benefit, ICIs are associated with various immune-related adverse events (irAEs), including dermatologic, gastrointestinal, hepatic,

endocrine, and pulmonary toxicities, which may necessitate treatment interruption or discontinuation (4,5). Furthermore, predictive biomarkers for response remain incompletely understood, particularly in breast cancer, which generally exhibits a relatively low tumor mutational burden (TMB) compared with other solid tumors such as melanoma or lung cancer (6). This biological feature may partly explain the variable efficacy of ICIs in breast cancer and highlights the need for further clinical evidence, especially in rare clinical settings.

Occult breast cancer (OBC), defined as axillary or distant lymph node metastasis without an identifiable primary tumor in the breast, is a rare clinical entity, accounting for less than 1% of all breast cancers (7-9). Due to its low incidence, the clinicopathological characteristics and optimal systemic treatment strategies for OBC remain poorly defined. In particular, evidence regarding the efficacy of ICI-containing regimens in OBC is extremely limited, and most available data are extrapolated from studies in non-occult TNBC.

Herein, we report a case of OBC with distant lymph node metastases that exhibited a sustained and marked response to Pembro combined with gemcitabine (GEM) and carboplatin (CBDCA). Although immune-related colitis developed during treatment, the Pembro-containing regimen was discontinued and treatment was switched to eribulin, the patient subsequently maintained long-term disease control under eribulin therapy. This case underscores the potential efficacy and management considerations of ICI-based therapy in rare breast cancer subtypes.

Case report

A 71-year-old woman presented with swelling of the left cervical region, which she first noticed several weeks before their initial visit to the Department of General Medicine, Saitama Medical University Hospital (Moroyama-machi, Japan) in July 2023. Contrast-enhanced computed tomography (CT) scans of the neck and chest revealed enlargement of multiple lymph nodes in the left axillary and supraclavicular regions. Fine-needle aspiration cytology of the left cervical lymph node revealed carcinoma. Positron emission tomography-CT using ^{18}F-fluorodeoxyglucose (FDG) demonstrated enlarged lymph nodes from the left cervical to axillary regions with increased FDG uptake (Fig. 1); however, no obvious primary lesion was detected. Breast ultrasonography was subsequently performed under the suspicion of axillary lymph node metastasis; however, no mass lesion was identified within the breast.

As an OBC was suspected, the patient was referred to the Department of Breast Oncology at our hospital for further evaluation. She had no significant past medical history and was taking only fexofenadine for seasonal allergic rhinitis. Regarding notable family history, their brother had gastric and colorectal cancers. The patient had no history of smoking or alcohol consumption, and had a known allergy to penicillin antibiotics.

Upon referral, a core needle biopsy of the axillary lymph node was performed. Histologically, the tumor cells showed marked nuclear atypia with pleomorphism. Immunohistochemistry (IHC) was performed using formalin-fixed, paraffin-embedded tissue sections (4 μm thick), and the primary antibodies, antigen retrieval methods and staining conditions are summarized in Table I. Immunostaining was performed using an automated immunostainer (BenchMark ULTRA PLUS; Roche Diagnostics) with a polymer-based detection system according to the manufacturer's protocol. The tumor cells were positive for mammaglobin, GATA-binding protein 3 and cytokeratin 7, and negative for gross cystic disease fluid protein-15 (GCDFP-15). ER and PgR expression rates were 0% and HER2 score was 0, supporting the diagnosis of metastatic TNBC of the axillary lymph node. Ki67 labeling index was 80% (Fig. 2). Based on these findings, the patient was diagnosed with OBC in the left breast, T0N3cM1(LYM), Stage IV TNBC. Programmed death-ligand 1 IHC demonstrated a combined positive score >10 with the 22C3 antibody, while the SP142 was IC0 (Fig. 2). Breast magnetic resonance imaging (MRI) was not performed because systemic therapy was prioritized in the setting of stage IV disease, and MRI could not be scheduled immediately.

Treatment with Pembro + GEM + CBDCA was initiated shortly after referral. The patient's height, weight, and body surface area were 150 cm, 43 kg, and 1.34 m^2, respectively. The administered doses were Pembro 200 mg, GEM 1,000 mg/m^2 (1,340 mg total dose), and CBDCA AUC 4 (165 mg, calculated using the Calvert formula). Even if the present case were classified as carcinoma of unknown primary site (CUP), this regimen was selected because GEM + CBDCA has been reported to be effective in CUP (10), and the KEYNOTE-355 trial demonstrated the clinical benefit of Pembro in combination with several standard chemotherapy regimens, including GEM + CBDCA, irrespective of chemotherapy partner (3). The chemotherapy course, including dose modifications, adverse events, and treatment responses, is summarized in Fig. 3. During the first cycle, the patient received Pembro + GEM + CBDCA on Day 1. On Day 8, the patient presented with elevated liver enzymes (AST 113 U/l; ALT 119 U/l, CTCAE Grade 2-3). Although immune-related hepatitis was considered, the abnormalities were primarily attributed to chemotherapy-induced toxicity, and the planned GEM + CBDCA was withheld for monitoring. On Day 15, the patient's liver function remained elevated (AST 64 U/l; ALT 82 U/l, Grade 1-2); thus, treatment was again postponed. In the second cycle, on Day 1, the treatment was delayed owing to a Grade 2 rash involving the neck, both sides of the forearms, and the dorsal and palmar surfaces of the hands. The patient was evaluated by a dermatologist; after considering differential diagnoses, including chemotherapy-induced reaction, drug eruption, infection, and contact dermatitis, the patient was treated with oral antihistamines and topical steroids. As the rash had improved to Grade 1 but persisted, Pembro was withheld as a precaution, whereas GEM + CBDCA were administered as scheduled. On Day 8, GEM + CBDCA were administered again as planned.

In the third cycle, on Day 1, the treatment was delayed owing to diarrhea (Grade 1). After improvement in the following week, Pembro was withheld due to concern for irAEs, whereas GEM + CBDCA were administered. On Day 8, GEM + CBDCA were also administered. However, from Day 9, the patient developed abdominal pain and Grade 2 diarrhea. By Day 15, she also presented with fever and was

Table I. Primary antibodies and staining conditions used for immunohistochemistry.

Name	Manufacturer	Cat. no.	Dilution	Antigen retrieval	Incubation temperature and time
GATA3	Nichirei Biosciences, Inc.	418201	Prediluted	pH 8.5, 95˚C, 64 min	36˚C, 32 min
GCDFP15	Leica Biosystems	NCL-L-GCDFP15	1:40	pH 8.5, 95˚C, 36 min	36˚C, 32 min
CK7	Agilent Technologies, Inc.	M7018	1:100	pH 8.5, 95˚C, 36 min	36˚C, 32 min
ER	Roche Diagnostics	790-4324	Prediluted	pH 8.5, 95˚C, 64 min	36˚C, 32 min
PgR	Roche Diagnostics	790-2223	Prediluted	pH 8.5, 95˚C, 64 min	36˚C, 32 min
HER2	Roche Diagnostics	790-2991	Prediluted	pH 8.5, 95˚C, 64 min	36˚C, 12 min
PD-L1 (22C3)	Dako; Agilent Technologies, Inc.	SK006	Ready-to-use	EnVision FLEX TRS low pH, 97˚C, 20 min	Room temperature, 30 min
PD-L1 (SP142)	Roche Tissue Diagnostics; Roche Diagnostics, Ltd.	744-7257	Prediluted	Cell Conditioning 1 (CC1; Roche Diagnostics) on the Ventana BenchMark ULTRA system	36˚C, 16 min

GATA3, GATA-binding protein 3; CK7, cytokeratin 7; GCDFP-15, gross cystic disease fluid protein-15; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1.

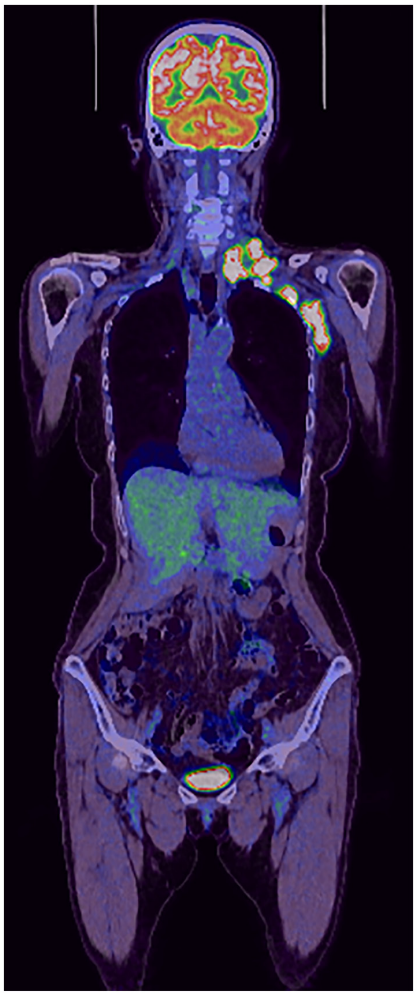

Figure 1. Enlarged lymph nodes from the left cervical to axillary regions showed increased ^{18}F-fluorodeoxyglucose uptake, with no identifiable primary breast lesion.

evaluated in our Department of Breast Oncology. Infectious enteritis was suspected; accordingly, the patient was initially managed as an outpatient and received symptomatic treatment, empiric levofloxacin (LVFX), and oral probiotics. However, as abdominal pain and diarrhea persisted, re-evaluation was performed on Day 18. Laboratory findings revealed white blood cell count of 6,610/μl and C-reactive protein level of 6.484 mg/dl. CT imaging demonstrated increased pericolic fat attenuation around the sigmoid and descending colon, indicative of colitis. Differential diagnoses included *Clostridioides difficile* (CD) colitis, other bacterial or viral enteritis, and other inflammatory bowel diseases. CMV antigen and stool tests, including CD antigen and CD toxin, yielded negative results.

Considering the possibility of irAE colitis, the patient was admitted on Day 18. During hospitalization, the patient continued oral LVFX and probiotics and was managed with bowel rest and intravenous fluids. Their symptoms improved by Day 21 (Day 3 of hospitalization); no systemic steroid therapy was required, and oral intake was resumed. The patient was discharged on Day 25 (Day 8 of hospitalization) after resolution of symptoms and stable oral intake. Colonoscopy performed 1 week after discharge revealed erosions in the transverse and sigmoid colon (Fig. 4A), and biopsy samples were obtained. Histopathology showed chronic inflammatory cell infiltration in the stroma and microcrypt abscesses (Fig. 4B), consistent with the diagnosis of ICI-related colitis.

Notably, CT performed during the third treatment cycle revealed marked shrinkage of the left axillary lymph node metastases, which decreased from 26 and 21 mm at baseline to 0 mm after treatment, as well as resolution of the left cervical lymph node metastasis, which decreased from 25 mm at baseline to 0 mm. According to RECIST criteria, both regions achieved a complete response (CR) to Pembro + GEM + CBDCA regimen (Fig. 5). The Pembro + GEM + CBDCA

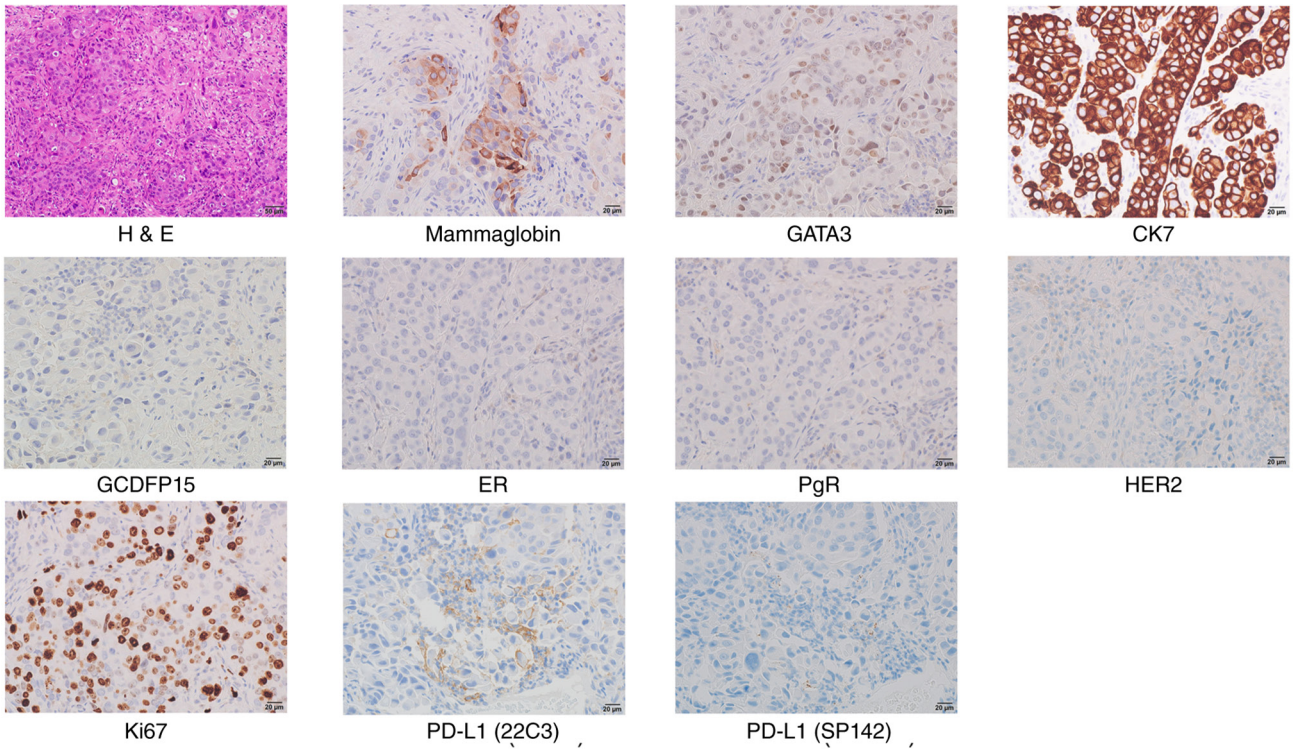

Figure 2. Histopathology and immunohistochemistry of the axillary lymph node metastasis. Representative images of the axillary lymph node core biopsy. H&E staining shows tumor cells with marked nuclear atypia and pleomorphism (magnification, x200; scale bar, 50 μm). Immunohistochemistry demonstrates positivity for mammaglobin, GATA3, and CK7, and negativity for GCDFP-15. Tumor cells are negative for ER, PgR and HER2 (triple-negative breast cancer profile), with a high Ki67 labeling index (80%), PD-L1 expression (22C3, CPS >10; SP142, IC0) (magnification, x400; scale bar, 20 μm). H&E, hematoxylin and eosin; GATA3, GATA-binding protein 3; CK7, cytokeratin 7; GCDFP15, gross cystic disease fluid protein-15; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor 2; PD-L1, programmed death-ligand 1.

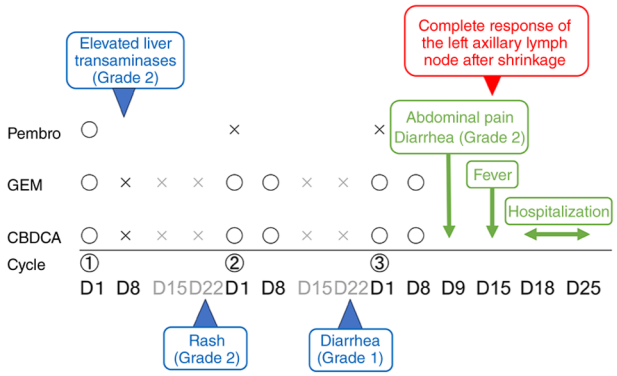

Figure 3. Treatment course and clinical response to Pembro + GEM + CBDCA. Timeline of three treatment cycles. Circles (□) indicate administered doses; crosses (x) represent omissions. Key events: Liver enzyme elevation (blue), Grade 2 rash and Grade 1 diarrhea (blue), and hospitalization (green double arrow). The red arrow shows the complete response of the left axillary lymph node on non-contrast CT. Dose delays/omissions with reasons are marked in blue. Pembro, pembrolizumab; GEM, gemcitabine; CBDCA, carboplatin; CT, computed tomography.

regimen was discontinued, and treatment was switched to eribulin 1 week after colonoscopy. Among the available options, including taxanes, eribulin, and oral fluoropyrimidines, we selected eribulin owing to its short infusion time and relatively low risk of gastrointestinal toxicity. Evidence guiding treatment after CR in this setting is limited, and data supporting a switch to maintenance systemic therapy remain scarce (11). The patient has continued regular follow-up visits at the time of each eribulin administration. Radiological evaluation using CT has been performed every 2-3 months to monitor disease status. The patient has maintained a CR on eribulin monotherapy for over 1 year as of February, 2026, the date of the most recent CT evaluation. Although breast MRI has not yet been performed, follow-up CT imaging has not demonstrated any detectable breast lesion.

Discussion

OBC is a rare clinical entity, accounting for less than 1% of all breast cancers. It is defined as axillary lymph node metastasis without an identifiable primary tumor in the breast on clinical and radiological examination (9). Originally, OBC was defined as axillary lymph node metastasis consistent with breast carcinoma without a clinically or radiologically detectable primary breast lesion. More recently, the definition has evolved with advances in imaging. For example, Ofri and Moore (9) proposed distinguishing clinical OBC from pathological OBC. They define clinical OBC as no lesion detectable on clinical examination, mammography, or ultrasonography, whereas pathological OBC additionally requires a negative breast MRI and, when performed, a pathologically negative mastectomy specimen. Given the absence of an apparent breast lesion, the differential diagnosis should include other primary malignancies known to metastasize to axillary lymph nodes, such as malignant melanoma, lung cancer, thyroid cancer, gastric cancer, colorectal cancer, pancreatic cancer, and ovarian cancer (12,13). Notably, accurate diagnosis relies

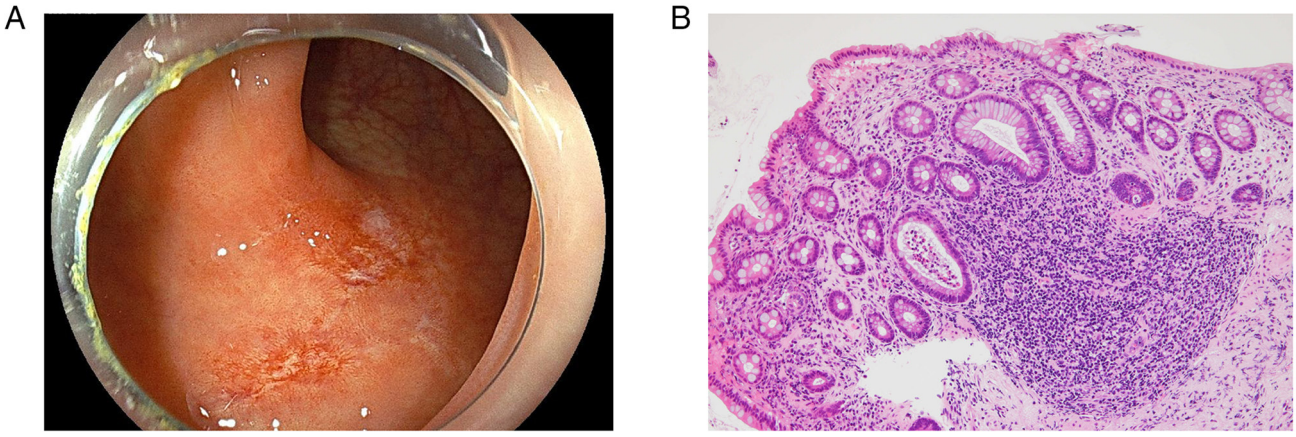

Figure 4. Representative colonoscopic and histopathological findings from the sigmoid colon. (A) Colonoscopic images showing erosions in the sigmoid colon. (B) Histopathological findings of the sigmoid colon biopsy showing chronic inflammatory cell infiltration in the stroma, focal lymphoplasmacytic accumulation, and microcrypt abscesses, consistent with mucosal injury (hematoxylin and eosin stain; magnification, x400).

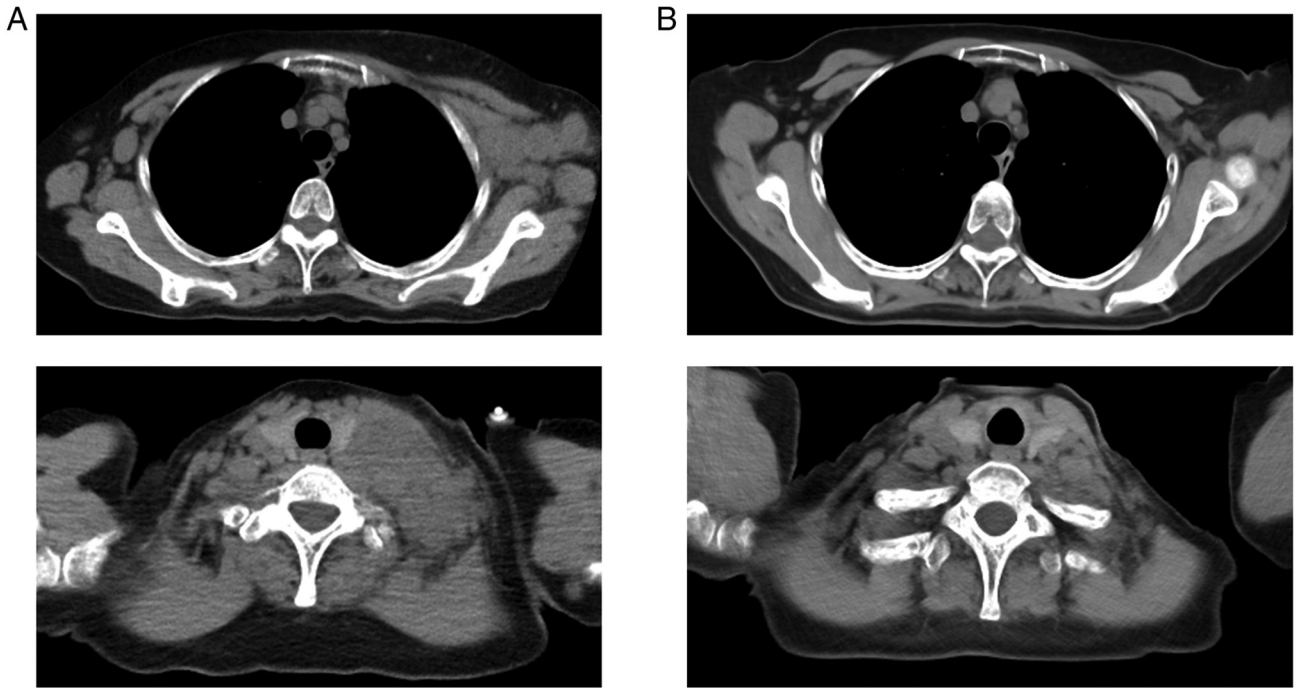

Figure 5. Comparison of non-contrast CT before and after therapy. (A) Axial baseline CT and (B) follow-up axial CT after three cycles of therapy. The upper panels show the left axillary lymph node region, and the lower panels show the left cervical lymph node region. Two left axillary lymph nodes decreased from 26 and 21 mm at baseline to 0 and 0 mm post-treatment, respectively, while the left cervical lymph node decreased from 25 mm to 0 mm, demonstrating a complete response in both regions. CT, computed tomography.

on thorough imaging and IHC evaluation of axillary lymph node metastases. IHC analysis of biomarkers, including ER, PgR, GCDFP-15, and mammaglobin, has proven useful in confirming that the tumor originates from breast tissue (14,15).

In the KEYNOTE-355 trial, irAEs occurred in approximately 26% of patients receiving Pembro in combination with chemotherapy. The most commonly reported irAEs included hypothyroidism, hyperthyroidism, pneumonitis, and colitis. Grade 3 or higher irAEs were relatively infrequent, occurring in approximately 5% of patients, with colitis reported in less than 1% (3). Regarding onset, patients receiving PD-1 monotherapy reportedly develop colitis at a median of 25.4 weeks (range: 0.6-119.9 weeks) after treatment initiation (16). The onset in the present case was relatively early compared with this previously reported median but was within the reported range, thereby indicating the possibility of early-onset cases. Therefore, when diarrhea occurs even after a limited number of Pembro administrations, immune-related colitis should be considered a differential diagnosis. In patients receiving combination therapy with ICIs and cytotoxic chemotherapy, alternative etiologies such as chemotherapy-induced mucosal injury, bacterial or viral infection, and pre-existing inflammatory bowel disease should also be considered (17). Systematic reviews have underscored the importance of timely colonoscopic evaluation in suspected ICI-induced colitis. Colonoscopy is generally recommended within 7 days of the

onset of moderate to severe diarrhea (grade ≥2), enabling direct mucosal assessment and biopsy to confirm diagnosis and exclude infections or other etiologies (5,18). Early colonoscopy facilitates accurate grading of inflammation, which guides treatment decisions. In cases with grade 2 or higher colitis, systemic corticosteroids are initiated promptly at doses of 1-2 mg/kg/day of prednisone or equivalent (4). Patients with severe symptoms (grade 3 or higher) or those unable to tolerate oral medications frequently require hospitalization for intravenous steroid administration and close monitoring (19). Steroid tapering over 4-6 weeks is recommended to reduce recurrence risk. In our case, infectious causes were excluded, and the patient's symptoms improved rapidly with bowel rest and hospitalization, allowing us to defer corticosteroid therapy. Colonoscopy and histopathological examination performed within 5 days of symptom onset confirmed the diagnosis of irAE colitis, highlighting the value of early endoscopic evaluation even in mild clinical courses.

Several studies have reported a positive association between irAE occurrence and ICI efficacy, including overall survival (OS). A meta-analysis published in 2021 demonstrated that patients who experienced irAEs had significantly higher response rates and improved OS than those who did not (20). These findings indicate that irAEs may serve as a surrogate marker for effective immune activation and therapeutic benefit. In our case, the emergence of irAEs may similarly reflect an active antitumor immune response, contributing to the favorable clinical outcome.

To the best of our knowledge, only few case reports have described a dramatic response to Pembro-containing chemotherapy in patients with metastatic or recurrent breast cancer (21). Given that breast cancer generally exhibits a low TMB, the efficacy of clinical ICIs in this setting has been considered limited (6). Preclinical studies suggest that tumor-draining lymph nodes play a central role in the antitumor activity of immune checkpoint blockade, serving as key sites for antigen presentation and T-cell priming (22,23). Consistent with this concept, clinical observations in gastric cancer have reported that nivolumab may be more effective in patients with lymphatic metastases (24). Similarly, in the present case, the predominant tumor burden consisted of lymph node metastases. Therefore, the lymph node-dominant disease distribution may have contributed to the favorable response to ICI therapy. However, evidence supporting this hypothesis in OBC is currently limited. Further studies are warranted to identify predictive biomarkers and clinical contexts where ICIs could provide meaningful benefit for patients with breast cancer.

This case has some limitations regarding diagnosis evaluation and treatment decision-making. In the present case, breast cancer was diagnosed based on ultrasonography, PET imaging, and pathological confirmation of metastatic breast carcinoma in the axillary lymph nodes. Mammography was not performed as the patient declined the procedure, and breast MRI could not be performed promptly owing to scheduling limitations. Therefore, this case did not fully meet the strict contemporary diagnostic criteria for OBC, as breast MRI is recommended by current guidelines (7,8) when conventional imaging is negative was not performed. The possibility of a small primary lesion detectable only by MRI cannot be completely excluded. Nevertheless, systemic therapy was prioritized because the patient had stage IV disease with lymph node metastases. Furthermore, repeated CT imaging during the clinical course did not demonstrate any breast lesions. Regarding irAEs, guidelines indicate that ICI therapy can generally be continued in patients with Grade 1 diarrhea (25-27). In the present case, Pembro was temporarily withheld after improvement of a preceding Grade 2 rash when Grade 1 diarrhea subsequently developed. Although the diarrhea was mild, the treatment was deferred owing to concerns of potential progression to immune-related colitis, prioritizing patient safety.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

WI and MO conceptualized and designed the study, and confirm the authenticity of all the raw data. KM, HI, TH, AO and TS contributed to the clinical management of the patient, participated in data acquisition and interpretation, and critically revised the manuscript. EM, TK, ANa, AS, AF, YI, ANu, AA, HS and HY performed the actual clinical treatments, and contributed to data collection and interpretation. YM performed pathological evaluations and contributed to data interpretation. All authors contributed to drafting the manuscript or critically revised it for important intellectual content, and read and approved the final version.

Ethics approval and consent to participate

The Institutional Review Board Saitama Medical University International Medical Center waived the ethical review of the current case report for which patient consent for publication was obtained.

Patient consent for publication

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

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to assist in literature search, and to identify relevant terminology and phrasing, and subsequently, the authors revised and edited

the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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