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Case Report

Acquired Treatment Resistance in a Patient with Metastatic PD-L1-Positive Breast Cancer and Germline BRCA1 Mutation

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Keywords
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Abstract
Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer associated with higher rates of relapse and mortality compared to other subtypes. Chemotherapy has been a mainstream treatment approach for TNBC due to the lack of therapeutic targets. Recent advances have led to the introduction of novel agents against specific patients with programmed death-ligand 1 (PD-L1)-positive TNBC who harbor germline *BRCA* mutations. However, some patients who respond to PD-L1 or poly (ADP-ribose) polymerase PARP inhibitors often develop resistance. Additionally, treatment strategies are more complicated for patients with PD-L1-positive TNBC and germline *BRCA* mutations. Here, we report a patient with metastatic PD-L1-positive TNBC who harbored a germline *BRCA1* mutation. The patient sequentially received combination treatment regimens, including PD-L1 inhibitors with chemotherapy and the PARP inhibitor olaparib, acquiring resistance to the treatments in a couple of months. Further investigations are warranted to elucidate the mechanisms underlying resistance to PD-L1 antibodies and PARP inhibitors to improve treatment outcomes while preventing emergence of treatment resistance in patients with TNBC.

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Introduction

Triple-negative breast cancer (TNBC), which accounts for 10–15% of all breast cancer cases, is an aggressive subtype that generally displays poorer prognosis compared to the other subtypes. TNBC is sensitive to chemotherapy, which has remained the standard of care despite its limited benefit [1]. Recent advances in the utility of novel agents have led to new treatments for certain patients with breast cancer such as those with germline *BRCA* mutations and those with programmed death-ligand 1 (PD-L1)-positive tumors. In the phase 3 OlympiAD trial, the (ADP-ribose) polymerase (PARP) inhibitor olaparib exhibited significant benefit over standard chemotherapy in patients with germline *BRCA*-mutated metastatic breast cancer [2]. In the phase 3 IMpassion130 study, the PD-L1 antibody atezolizumab plus nab-paclitaxel prolonged progression-free survival and overall survival in patients with metastatic PD-L1-positive TNBC [3]. In the phase 3 KEYNOTE-355 study, the PD-L1 antibody pembrolizumab plus chemotherapy showed significant improvement in progression-free survival compared to placebo plus chemotherapy in patients with metastatic PD-L1-positive TNBC [4]. Therefore, treatment strategies are complicated in patients with PD-L1-positive TNBC and germline *BRCA* mutation. A widely used strategy in cancer immunotherapy is established on the basis of the combination of immune checkpoint inhibitors with each other or with other anticancer agents, including systemic chemotherapy, PARP inhibitors, and targeted therapies [5]. Additionally, one study reported the presence of a crosstalk between PARP inhibition and the PD-L1/programmed death-1 immune checkpoint axis based on the observation that PARP inhibition upregulated PD-L1 expression and enhanced cancer-associated immunosuppression [6]. However, only a small subset of those patients who respond to immune checkpoint or PARP inhibitors often develop resistance. Here, we report the case of a patient with metastatic PD-L1-positive TNBC who harbored a germline *BRCA1* mutation and sequentially received treatment with immune checkpoint inhibitors and the PARP inhibitor olaparib.

Case Report

A 34-year-old woman was diagnosed with left breast cancer, which was determined as stage 2A (T2N0M0). The specimen obtained from the primary breast cancer was negative for HER2, estrogen receptor (ER), and progesterone receptor with immunohistochemical evaluation. The combined positive score for PD-L1 (clone 22C3) expression was 30%, and PD-L1 (clone SP142) expression on tumor-infiltrating immune cells as a percentage of tumor area accounted for 10% (Fig. 1). Breast-conserving surgery and sentinel lymph node biopsy were performed. The patient underwent standard radiotherapy, and 4 cycles of adjuvant chemotherapy with docetaxel and cyclophosphamide were administered.

Four years later, the patient was diagnosed with contralateral breast cancer, which was determined as stage 2A (T2N0M0). Immunohistochemistry confirmed that the tumor was negative for HER2 and progesterone receptor and 10% positive with weak stain intensity for ER. Mastectomy and sentinel lymph node biopsy were performed, and axillary dissection was added during surgery because of metastasis detected in the sentinel lymph node. The patient received 4 cycles of doxorubicin and cyclophosphamide as adjuvant chemotherapy. Subsequently, tamoxifen and gonadotropin-releasing hormone agonist were provided as adjuvant endocrine therapy because of slight positivity for ER. In the patient's extended family, the sister was the only person with a history of breast cancer. The patient was evaluated using BRACAnalysis® (Myriad Genetics, Salt Lake City, UT, USA), which revealed that the patient harbored a *BRCA1* variant (c.2192_2196del).

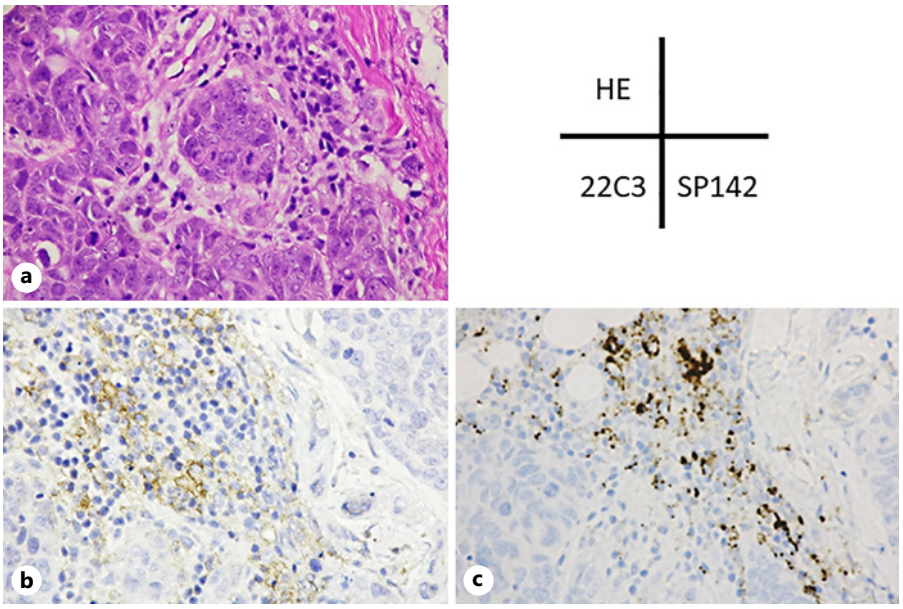

Fig. 1. Histological findings of invasive ductal carcinoma with programmed death-ligand 1 (PD-L1) positivity. **a** Hematoxylin and eosin staining showing invasive ductal carcinoma. **b, c** Immunohistochemistry images showing expression of PD-L1. **b** PD-L1 (clone 22C3). **c** PD-L1 (clone SP142).

Five and a half years after the left breast surgery, positron emission tomography/computed tomography revealed multiple lung metastases, pleural dissemination, pleural effusion, and supraclavicular node metastasis (Fig. 2). A biopsy was not repeated owing to the absence of a suitable target for re-biopsy and the patient's condition was critical enough to warrant immediate treatment administration. Atezolizumab and nab-paclitaxel were administrated as first-line therapy. The level of cancer antigen 15-3 (CA15-3), which gradually decreased during the first 3 months of treatment, was found to be elevated during evaluation 4 months after the administration of atezolizumab and nab-paclitaxel. Computed tomography revealed disease progression (Fig. 3, 4a, b). Olaparib was administrated as second-line therapy, and the CA15-3 level declined to 22 U/mL which was below the upper limit 3 months after the start of olaparib. However, the CA15-3 level increased again and liver metastasis was found 4 months after the administration, although pleural effusion had subsided (Fig. 4c). Two cycles of pembrolizumab, gemcitabine, and carboplatin were administered as third-line therapy; however, the CA15-3 level rose rapidly and computed tomography revealed the growth of liver metastasis, suggesting that the treatment failed (Fig. 3, 4d). Subsequently, the patient received, in order of administration, eribulin for 2 months, olaparib rechallenge in addition to whole-brain irradiation for multiple brain metastases for 2 weeks, and TS-1 for 1 month. The patient also received medical palliative care and subsequently died 15 months after recurrence. After the failure of olaparib, the disease was resistant to any of the subsequent treatments including pembrolizumab plus chemotherapy.

Discussion

Pathogenic variants of *BRCA1* and *BRCA2* were associated with increased risk of ovarian and breast cancers [7]. The *BRCA* genes encode proteins associated with the homologous recombination repair of double-strand DNA breaks. Pathogenic *BRCA* variants are sensitive to

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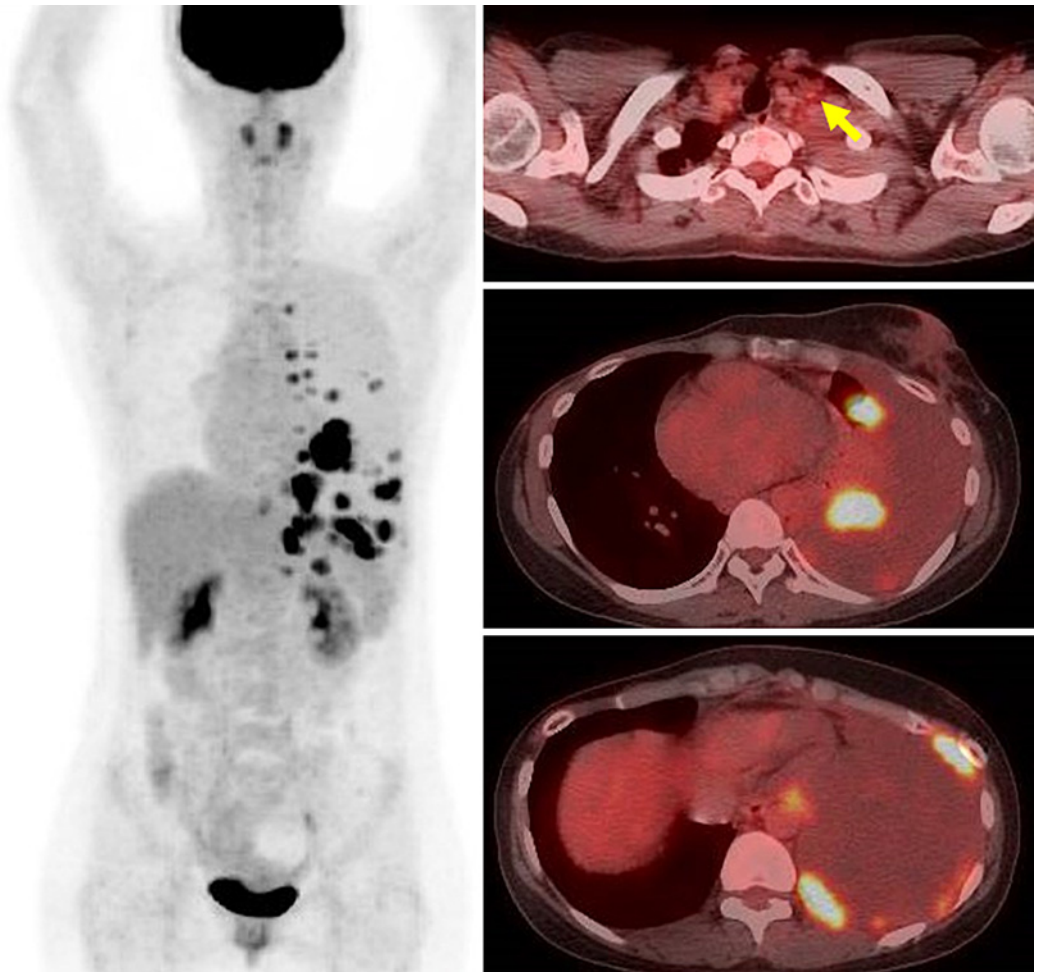

Fig. 2. Positron emission tomography/computed tomography image showing multiple lung metastases, pleural dissemination, pleural effusion, and supraclavicular node metastasis. The arrow indicates the supraclavicular node metastasis.

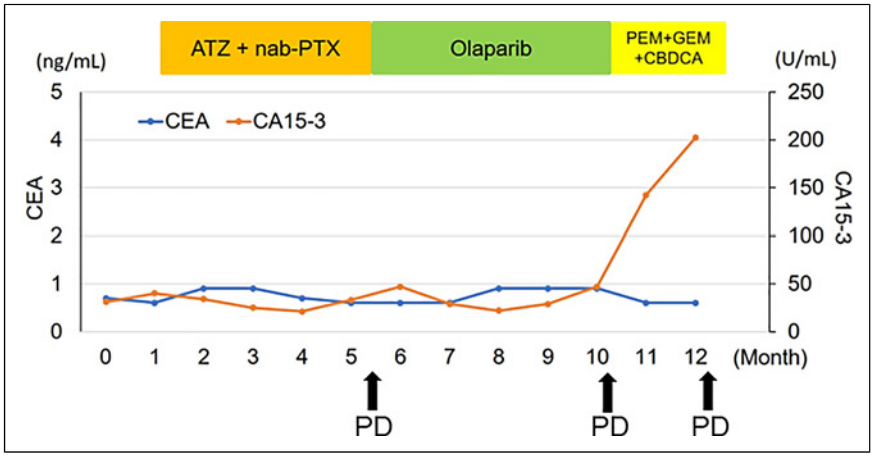

Fig. 3. Changes in the levels of cancer antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) from the first-line treatment to the end of the third-line treatment.

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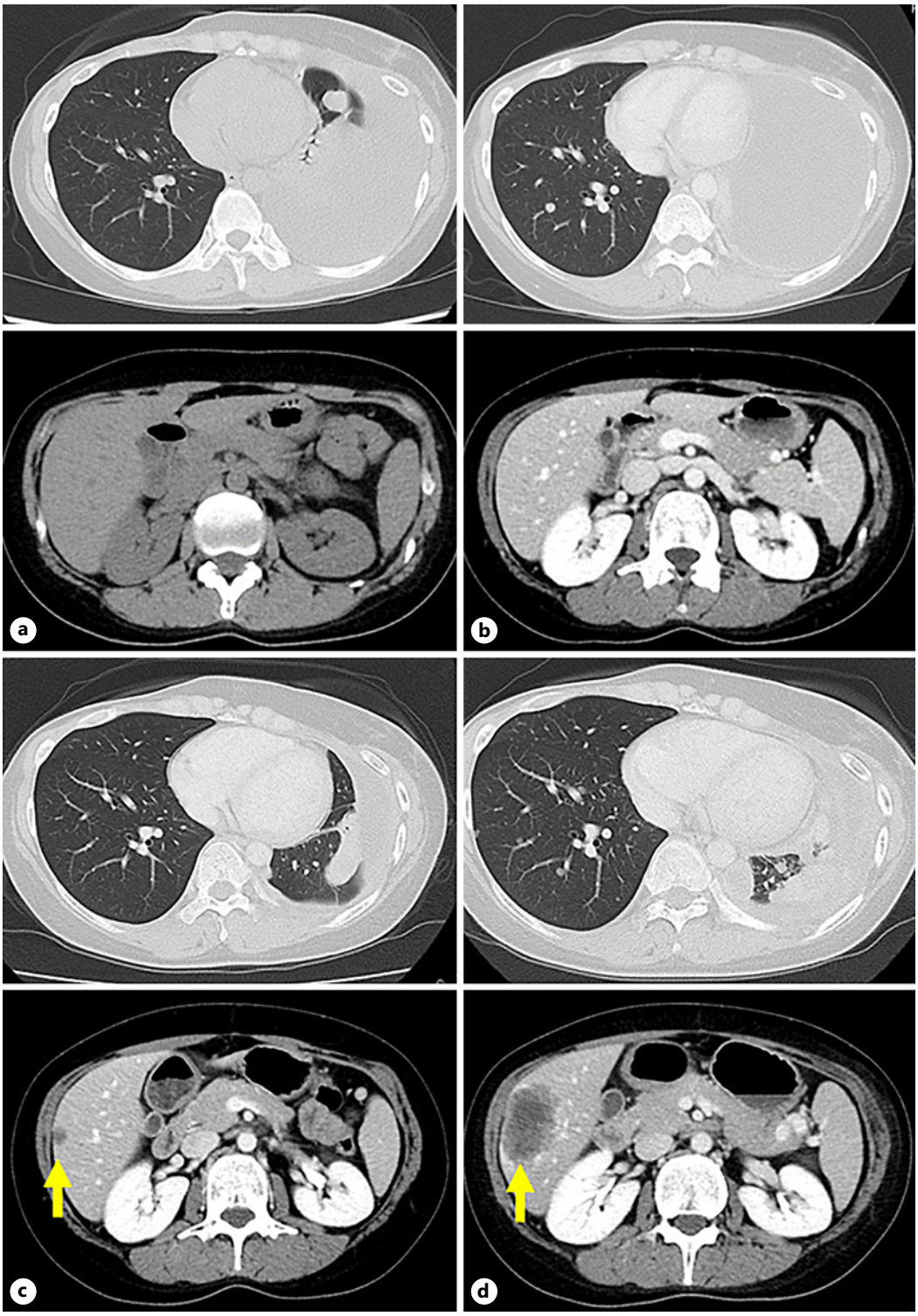

Fig. 4. Computed tomography images showing lung metastases, pleural dissemination, pleural effusion, and liver metastasis during the course of treatments. **a** Before the administration of atezolizumab plus nab-paclitaxel. **b** After 4 months of treatment with atezolizumab plus nab-paclitaxel. **c** After 4 months of treatment with olaparib. **d** After 2 months of treatment with pembrolizumab plus gemcitabine plus carboplatin. The arrow indicates liver metastasis.

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PARP inhibition via multiple mechanisms, including PARP trapping on DNA at sites of single-strand breaks, which cannot be repaired accurately in tumors showing defects in homologous recombination repair, resulting in synthetic lethality [8]. Therefore, PARP inhibitors result in the accumulation of DNA damage in tumor cells with deficient DNA damage repair, thereby causing tumor cell death [9]. The PARP inhibitor olaparib was reported to be clinically effective in patients with breast cancer harboring germline *BRCA* mutations in the OlympiAD trial [2]. The study included 302 patients with metastatic breast cancer and *BRCA* mutations who were administered anthracycline and taxane in an adjuvant or metastatic setting and no more than two previous chemotherapy regimens for metastatic disease. The patients who were randomly assigned to receive treatment with olaparib experienced improved progression-free survival relative to those who received standard therapy with the treating physician's preferred single-agent chemotherapy [2].

The rate of TNBC was 62.2% among patients with *BRCA1* mutations, suggesting that breast cancer occurring in carriers of *BRCA1* mutations is more likely to be triple-negative [10]. The IMpassion130 trial revealed that there was no significant difference in overall survival between atezolizumab plus nab-paclitaxel group and placebo plus nab-paclitaxel group in the intention-to-treat population but suggested a clinically meaningful overall survival benefit with atezolizumab plus nab-paclitaxel in patients with PD-L1 immune cell-positive unresectable, locally advanced, or metastatic TNBC [3]. The phase 3 KEYNOTE-355 trial revealed progression-free and overall survival benefit from the addition of pembrolizumab to first-line standard-of-care chemotherapy in patients with advanced-stage TNBC with a PD-L1 combined positive score of ≥10 [4].

The current patient harboring a germline *BRCA1* mutation with PD-L1-positive TNBC received, in order of administration, atezolizumab plus nab-paclitaxel, olaparib, and pembrolizumab in combination with gemcitabine and carboplatin. Atezolizumab plus nab-paclitaxel and olaparib temporarily impeded disease progression, which was not affected by the treatment with pembrolizumab plus chemotherapy either, indicating that none of the three treatments sufficiently controlled disease progression. The disease acquired resistance to immune checkpoint inhibitors, chemotherapy, and PARP inhibitors early after diagnosis. Current literature, albeit limited, indicates that resistance to immune checkpoint inhibitors might be associated with several factors, including mutations in tumor antigens and molecules involved in antigen presentation, multiple immune checkpoint interactions, dynamic changes in the immune microenvironment, activation of oncogenic pathways, gene mutations and epigenetic changes of key proteins in tumor cells, competitive tumor metabolism, and accumulation of metabolites [11]. On the other hand, one study reported that PD-L1 expression was upregulated by PARP inhibition, providing evidence to support the combination of PARP inhibitors and PD-L1 antibodies as a potential therapeutic approach to treat breast cancer [6]. In fact, several ongoing clinical trials are testing the combination of PARP inhibitors and PD-L1 or programmed death-1 antibodies in multiple cancer types. In the present case, the combination of olaparib with atezolizumab or pembrolizumab might provide more benefit to the patient [6].

Similar to what is observed with other chemotherapy agents, patients can develop resistance to PARP inhibitors. As an essential prerequisite of synthetic lethality, failure of homologous recombination repair plays a pivotal role in tumor cell death, and the restoration of this repair mechanism is a predominant mechanism underlying PARP inhibitor resistance. Various factors, such as DNA replication fork protection, reversion mutations, epigenetic modifications, restoration of ADP-ribosylation (i.e., PARylation), and pharmacological alterations can lead to PARP inhibitor resistance [12]. Wang et al. [13] reported that *BRCA1* frameshift mutations in exon 11 could also partially compensate for wild-type *BRCA1* in response to PARP inhibitors, resulting in limited benefit from PARP inhibitors. In the present

case, the germline *BRCA1* mutation (c.2192_2196del) leading to a frameshift mutation in exon 11 might be one of the reasons underlying the acquired resistance to olaparib in 4 months.

In the present case, the cancer genome panel (CGP) test such as FoundationOne liquid was not checked. This test could have been performed before pembrolizumab was used after progression to olaparib. CGP might reveal actionable mutation or help clinicians solve an acquired resistant mechanism. A re-biopsy was not performed in this case. Even if re-biopsy had been performed and the result had revealed slightly positive for ER or negative for PD-L1, the combination of immune checkpoint inhibitor and chemotherapy would be provided based on primary tumor subtype in first-line therapy because her condition was critical and the Impassion130 trial assessed PD-L1 expression on primary tumors (60% of patients) and metastatic lesions (40% of patients), and efficacy of treatment appeared to be similar. However, immune checkpoint inhibitors would not be used in third line if re-biopsy outcomes were positive for ER. Performing a re-biopsy should be considered if possible. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530131).

In conclusion, we reported the case of a patient with metastatic PD-L1-positive TNBC who harbored a germline *BRCA1* mutation. She received sequential treatment with immune checkpoint and PARP inhibitors, although the benefit of these treatments was limited. Although concomitant treatment with PARP inhibitors and PD-L1 antibodies might provide more benefit compared to sequential therapy with the same drugs, further investigation is warranted to elucidate the mechanism of resistance to PD-L1 antibodies and PARP inhibitors.

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Statement of Ethics

Written informed consent was obtained from the patient's spouse for publication of this case report and any accompanying images. Ethical approval was not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding source to report.

Author Contributions

R. Matsunuma and T. Kumeta wrote the main manuscript. K. Yamaguchi, R. Hayami, K. Arai, and M. Tsuneizumi contributed to interpretation of data and critically revised the manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

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