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CLINICAL CASE REPORT

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Liver Metastasis of a Triple-Negative Breast Cancer and Complete Remission for 5 Years After Treatment With Combined Bevacizumab/Paclitaxel/Carboplatin

Case Report and Review of the Literature

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Abstract: Triple-negative breast cancer (TNBC) is aggressive, with high risk of visceral metastasis and death. A substantial proportion of patients with TNBC is associated with *BRCA* mutations, implying that these tumors are sensitive to DNA-damaging agents. We report successful treatment of a metastatic TNBC in a woman with a *BRCA2* germline mutation using combined bevacizumab/paclitaxel/carboplatin (BPC) therapy. The patient was pregnant and had liver metastases, and a complete clinical response was sustained for approximately 5 years. Mastectomy was performed during the 29th week of pregnancy, and the baby was later delivered by caesarean section. Subsequently, multiple metastases in both liver lobes were detected using computed tomography and magnetic resonance imaging and the patient was treated with a BPC regimen, which led to complete disappearance of metastatic lesions in the liver. No additional treatment was provided, and after 5 years the patient consented to direct sequencing of *BRCA2* and a 6781delG mutation was identified. At the most recent (5-year) follow-up, the patient was alive with good quality of life and no evidence of metastases.

This finding suggests that BPC therapy might be considered a good therapeutic option for the treatment of metastatic TNBC in a woman with a *BRCA2* germline mutation.

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Abbreviations: BPC = bevacizumab/paclitaxel/carboplatin, CR = complete remission, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, NSCLC = nonsmall cell lung cancer, ORR = overall response rate, PFS = progression-free survival, PgR = progesterone receptor, TNBC = triple-negative breast cancer.

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BACKGROUND

Triple-negative breast cancer (TNBC) is defined by the absence of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) expression, and has a highly aggressive nature. Accordingly, recurrence usually develops between 1 and 3 years after the initial diagnosis and most deaths occur within 5 years.[1–3] Despite poor prognosis, TNBC is characterized by molecular mechanisms that have potential as therapeutic targets, including abnormalities in DNA repair mechanisms, and a propensity toward neoangiogenesis.[4] DNA repair defects are characteristic of *BRCA* mutant cancers, which are present in 25% of patients with TNBC[5] and confer sensitivity to DNA damaging agents.[6] Bevacizumab is a target therapy for vascular endothelial growth factor, which suppresses tumor growth by inhibiting neoangiogenesis. Moreover, in a large-scale clinical trial of metastatic TNBC patients, bevacizumab improved overall response rates (ORR) and progression-free survival (PFS) in combination with conventional chemotherapy.[7]

Accordingly, the combination of bevacizumab, paclitaxel, and carboplatin (BPC) has been approved for patients with progressive metastatic nonsmall cell lung cancers (NSCLC), and significant improvements in survival rates have been demonstrated.[8]

In this report, we describe the successful use of BPC therapy in the treatment of metastatic TNBC in a woman with a *BRCA2* germline mutation. Complete remission (CR) was achieved without additional treatment and the patient remained disease-free after 5 years.

CASE PRESENTATION

Our institutional review board considered the approval was not required for this case report since written informed consent was obtained from the patient.

In June 2009, a 34-year-old woman was diagnosed with cancer of the right breast during her 28th week of pregnancy. Her family included several members with breast cancer and 1 with prostate cancer, suggesting likely genetic dispositions. Mastectomy was performed during the 29th week of pregnancy and axillary lymph nodes were resected. Subsequent pathological examinations of the surgical specimen revealed an invasive ductal carcinoma of 28 × 20 mm with the diagnostic characteristics ly+, v+, nuclear grade 2, lymph node metastasis (level I

1/10), ER-negative, PgR-negative, and HER2-negative. The fetus was developing normally immediately before surgery, with appropriate-for-date fetal weight of 1552 g at 29 weeks of gestation. In August 2009, a caesarean section was performed at 35 gestational weeks and a male with no physical or neurological abnormalities was delivered (birth weight 2311 g and APGAR scores of 7 and 8 at 1 and 5 min, respectively). Although temporary artificial respiration was required, the infant's development was normal and he was discharged from the hospital at 45 days after delivery.

Abdominal computed tomography scans of the patient were performed immediately after delivery, and multiple low-density masses were detected in both liver lobes (Figure 1). Subsequent abdominal magnetic resonance imaging indicated the presence of liver metastases of the breast cancer (Figures 2 and 3). Thus, a multidisciplinary discussion involving breast surgeons, hepato-biliary-pancreatic surgeons, oncologists, obstetricians, radiologists, pathologists, and nursing staff was held to formulate a management plan for the patient, and systemic therapy containing bevacizumab was prescribed. Although the patient accepted the decision, bevacizumab had not been approved in Japan for the treatment of breast cancer at that time (August 2009). Because our hospital is licensed only to provide medical care that is underwritten by the national healthcare system, it was not possible to offer this treatment. Therefore, the patient was referred to a facility that was not underwritten by the national healthcare system, and BPC therapy was initiated on August 27, 2009. Upon commencement of treatment, lung, liver, kidney, and heart functions were all within normal limits, and the patient's Eastern Cooperative Oncology Group performance status was 0.

Therapy comprised intravenous administration of 6 courses of BPC over a 28-day cycle, and 2 mg/kg bevacizumab was administered on days 1 and 8, followed by 4 mg/kg on day 15. Paclitaxel (80 mg/mm^2) was administered on days 1, 8, and 15, and carboplatin (area under the curve, 2.0 mg/mL per min) was administered on days 1, 8, and 15. Neoplastic lesions had disappeared after completion of the sixth course of BPC and cavitation was observed in S7 of the metastatic lesions. Side effects during therapy included grade 3 leukopenia, grade 1 peripheral neuropathy, general lethargy, and diarrhea, but no fever occurred during therapy. In 2014, the patient consented to direct genetic sequencing of the *BRCA2* gene and a 6781delG mutation was identified. After completion of the sixth course of BPC therapy, no other additional treatment was given. At the most recent follow-up in 2014 (5 years after the start of treatment), no recurrence of liver lesions (Figures 2 and 4) or new metastases to any other area were observed (Figure 5) and the patient reported a good quality of life.

DISCUSSION

In 2009, when we began treating the present patient, it was accepted that conventional chemotherapy was less effective for metastatic TNBC than for other metastatic breast cancers, and resulted in worse prognosis.[9,10] All treatment policies, including surgical approaches for liver metastases, were discussed by the multidisciplinary team. Although no studies of BPC therapy for breast cancer were available, subgroup analyses in small-scale studies of platinum agents[11] and targeted therapies[12] indicated efficacy in the treatment of metastatic TNBC. Moreover, the clinical safety of this regimen was sufficiently demonstrated in patients with metastatic and recurrent NSCLC.[8] Thus, BPC therapy was prescribed for the patient.

The effects of platinum agents in *BRCA* mutant breast cancers have been examined in several reports that were published after completion of the present BPC regimen. These indicate that whereas platinum agents are not effective in all

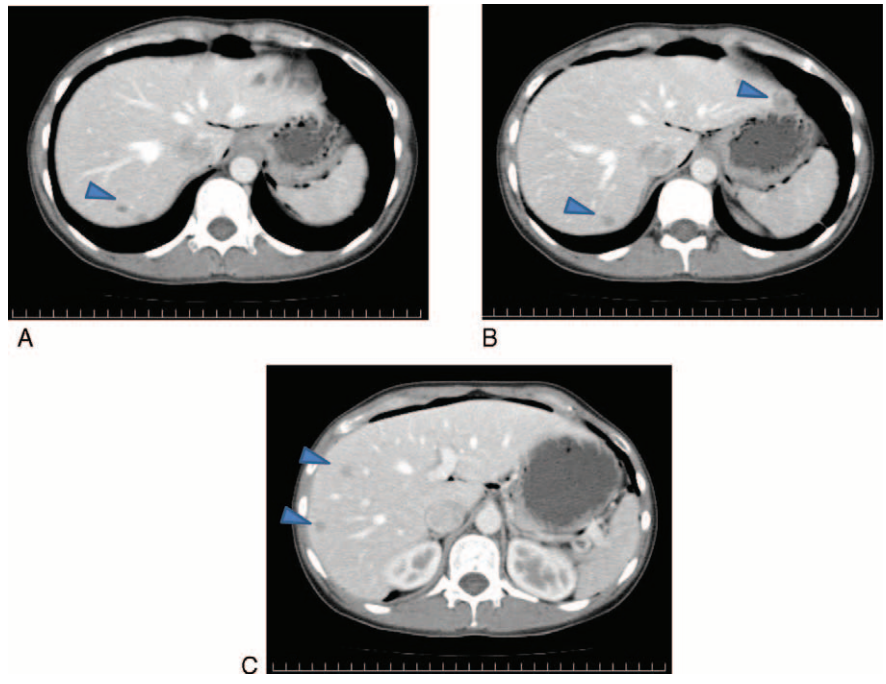

FIGURE 1. Contrast-enhanced computed tomography images from before the start of bevacizumab/paclitaxel/carboplatin therapy in 2009. Low-density masses are visible in both liver lobes: (A) low-density masses in S7, (B) low-density masses in S2 and S7, and (C) low-density masses in S8 (arrows indicate lesions).

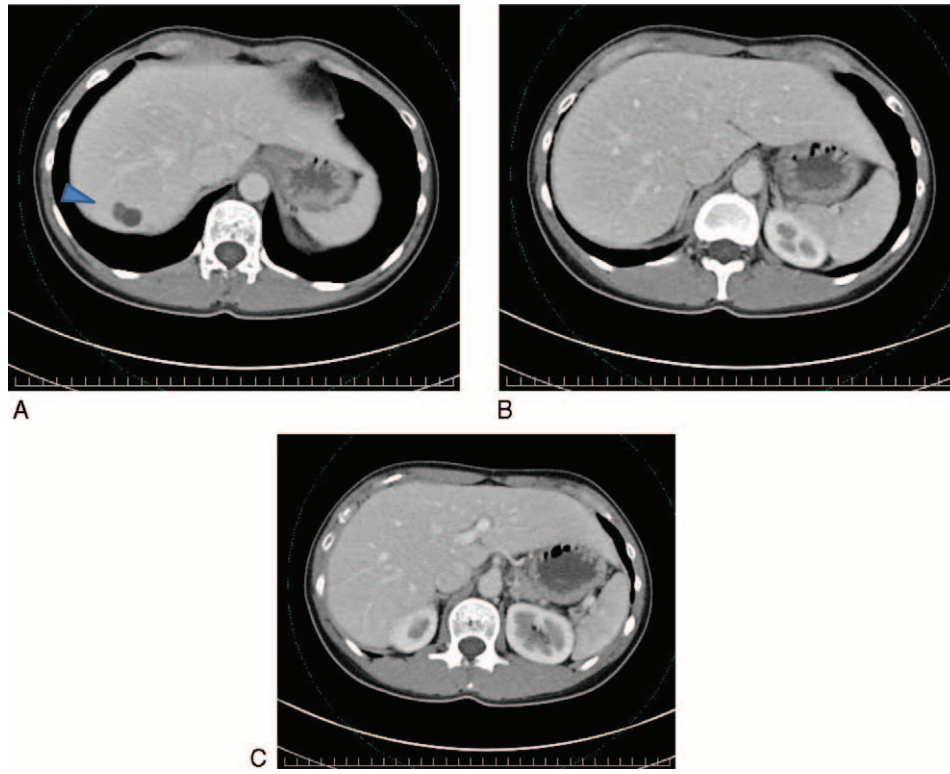

FIGURE 2. Contrast-enhanced computed tomography images from after the completion of bevacizumab/paclitaxel/carboplatin therapy in 2014. Metastatic lesions were replaced by visible cavitations in S7 (arrows indicate cavitations; (A), which subsequently disappeared (B and C).

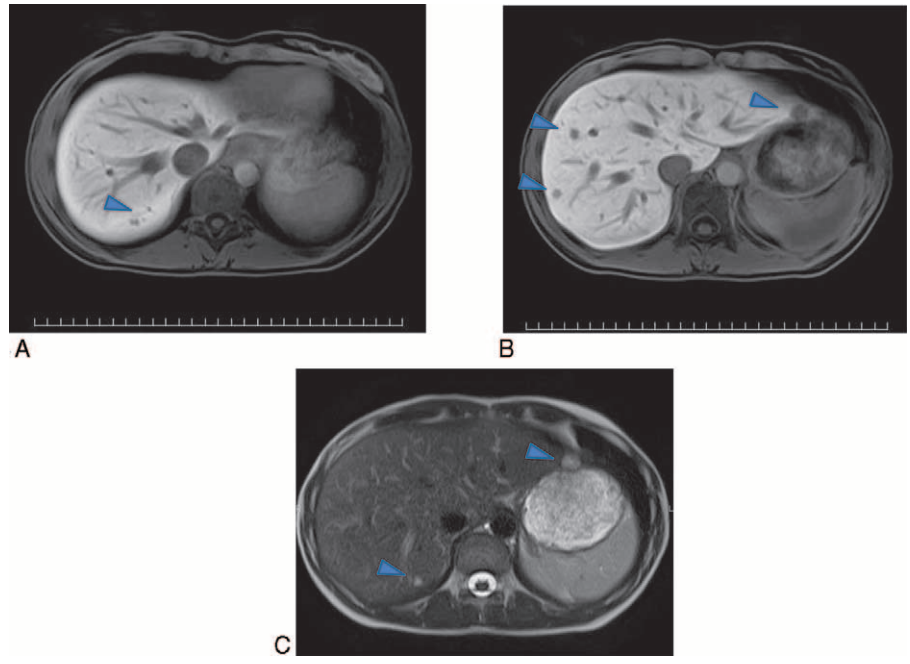

FIGURE 3. Magnetic resonance (MR) images from before the start of bevacizumab/paclitaxel/carboplatin therapy in 2009. etoxybenzyl-MRI images of hepatocytes; low-intensity masses are visible in the same region shown in the computed tomography image; low-intensity masses in S7 (A) and low-intensity masses in S2 and S8 (B). T2-weighted image; high-intensity masses are visible in S7 and on the surface of the left lobe of the liver (C). These imaging results indicate liver metastasis of breast cancer (arrows indicate lesions).

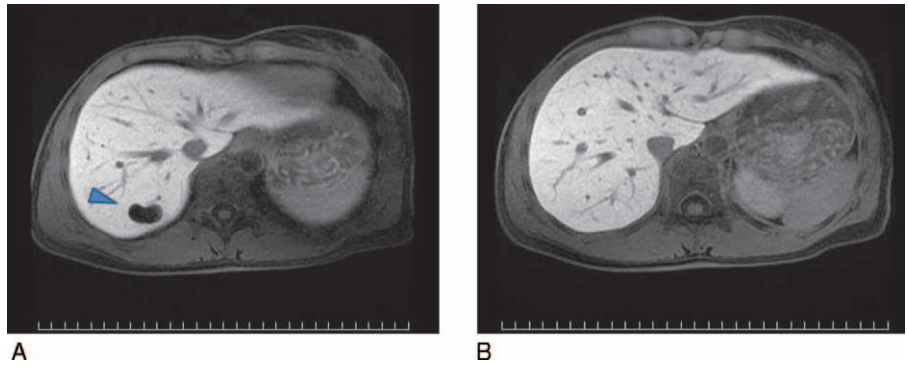

FIGURE 4. Magnetic resonance images from after the completion of bevacizumab/paclitaxel/carboplatin therapy in 2014. Metastatic lesions were replaced by visible cavitations in S7 (arrows indicate cavitations; A) and subsequently disappeared (B).

cases of TNBC,[13] good results have been achieved in with the presence of *BRCA1* mutations.[14,15] Because *BRCA* mutations are present in only a small proportion of breast cancer cases,[5] relatively small numbers of these patients have been included in previous analyses. However, preoperative chemotherapy with cisplatin alone reportedly resulted in pathologic complete response rates of 90%[11] and 100%,[14] and a recent prospective study of cisplatin monotherapies demonstrated a preoperative pathologic complete response rate of 61% in 107 *BRCA1*-mutant patients.[16] In another study of metastatic breast cancer patients with *BRCA1* germline mutations, treatment with cisplatin alone yielded an ORR of 80% and a complete response rate of 45%, even though 50% of patients had received prior chemotherapy.[17] Moreover, a previous study showed that anthracyclines achieved better results among patients with *BRCA2*-related breast cancers than among those with *BRCA1*-related breast cancers.[18] Although the data from this study were limited, *BRCA1* and *BRCA2* have similar DNA repair functions and comparable ovarian cancer treatment effects were observed in patients with *BRCA1* and *BRCA2* mutations. In contrast, poly(ADP-ribose) polymerase was specifically effective against *BRCA2*-related breast cancers. Taken together, these studies suggest that *BRCA1*- and *BRCA2*-related breast cancers respond similarly to certain treatment regimens.

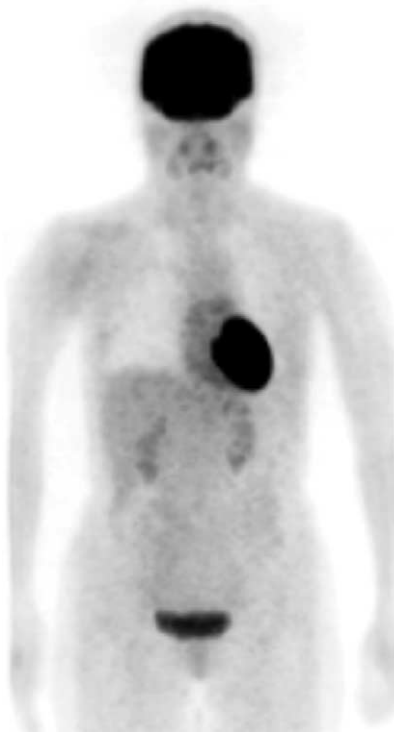

FIGURE 5. Full-length positron emission tomography image showing the absence of metastatic lesions.

Previous analysis of 585 patients with metastatic TNBC from the ATHENA study showed a response rate of 49%, a complete response rate of 10%, PFS of 7.2 months, and a 1-year survival rate of 60% after combined treatments with bevacizumab and taxane agents.[7] Moreover, in a meta-analysis of the E2100, AVADO, and RIBBON trials, addition of bevacizumab to initial chemotherapies for TNBC patients led to improved median PFS (8.1 months), response rates (42%), and 1-year survival (71%) compared with chemotherapy alone.[19]

Small-scale studies also report superior results using 3-agent approaches to TNBC, in which platinum agents were added to molecular targeted therapies and conventional chemotherapies as in the present case. Specifically, in a phase II clinical trial of preoperative chemotherapy comprising carboplatin, bevacizumab, and docetaxel for TNBC patients, a pathological complete response rate of 42% ($n = 19$) and a clinical response rate of 96% ($n = 43$) were achieved.[20] Another phase II clinical trial of combined carboplatin, bevacizumab, and nab-paclitaxel treatments for patients with metastatic TNBC achieved a median PFS of 9.2 months, a clinical benefit rate of 94%, and a response rate of 85%,[21] further indicating the benefits of bevacizumab co-treatments for patients with TNBC.

The BPC regimen is reportedly effective in cases of progressive, metastatic, and recurrent NSCLC,[8] and although no previous studies report the effects of this regimen in breast cancer patients, platinum agents have been effective in patients with *BRCA* mutations.[16,17] Finally, the reported effectiveness of bevacizumab in combination with taxane and platinum agents for the treatment of TNBC cases provides further evidence of the beneficial effects of platinum agents.[20,21]

It is unclear whether the long-term CR (5 years after the start of treatment) in our patient reflects the efficacy of bevacizumab, the platinum agent, or the taxane agent, and to what extent synergistic effects are responsible. In a previous study, 4 *BRCA1*-positive metastatic breast cancer patients survived for

50 to 62 months after treatment with cisplatin, although progression occurred after 28 to 36 months in these patients, and additional chemotherapy was administered.[17] In the present patient, cavitation in the liver appeared after the disappearance of metastases, potentially indicating the effects of bevacizumab. However, in the aforementioned meta-analysis of E2100, AVADO, and RIBBON trials, no patients achieved a long-term (5-year) CR with first-line treatment alone,[19] and second-line therapies were administered upon disease progression. Moreover, median overall survival was 20 months among patients treated with first-line chemotherapy plus bevacizumab for liver metastases from *HER2*-negative breast cancers.[22]

Although surgical treatment was not selected for the present patient, recent retrospective studies support surgical approaches for patients with liver metastases of breast cancers,[23–26] and indicate better outcomes of surgical treatments than chemotherapy alone. Hence, surgery can achieve survival benefits and prolonged remission in patients with good responses to systemic therapy. Accordingly, surgery may be considered in the event of recurrent liver metastasis in the present patient.

CONCLUSIONS

No previous studies have investigated the use of BPC for the treatment of patients with TNBC associated with *BRCA1/2* germline mutations. However, the present encouraging case warrants clinical studies of the efficacy of BPC therapy in this population.

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