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Case Report

# Positive Therapeutic Response to Bevacizumab Plus Paclitaxel in a Patient with Advanced, Life-Threatening Breast Cancer and Carcinomatous Lymphangitis : a Subsequent Treatment Change to Hormone Therapy

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**SUMMARY**

We present a case of advanced, life-threatening breast cancer with carcinomatous lymphangitis treated with bevacizumab plus paclitaxel. A positive therapeutic response was achieved and the treatment was subsequently changed to hormone therapy.

The patient was a 53-year-old postmenopausal woman with a non-contributory medical history. She presented to a nearby hospital with chief complaints of continued exertional dyspnea and coughing since March 2012. Physical findings included a palpable mass in the left breast, and the patient was referred and presented to our hospital in May. Examinations at our hospital revealed left-sided breast cancer (estrogen receptor positive, progesterone receptor positive, and no amplification of the human epidermal growth factor receptor 2 by FISH). The patient had bone metastasis and carcinomatous lymphangitis (cT2N3cM1-stage IV). The condition was life threatening, and administration of bevacizumab plus weekly paclitaxel was initiated with the expectation of a high response rate. Coughing and dyspnea resolved two weeks later. CT scans were taken in August after the completion of 3 cycles and showed improvement in carcinomatous lymphangitis. No major side effects were observed due to bevacizumab plus weekly paclitaxel. When the CT scans were taken in December after the completion of 6 cycles, the primary lesion and lymph node metastases were reduced in size. In the lung field, there was no thickening of the interlobular septa or subpleural interstitium, and the findings of carcinomatous lymphangitis were improved. Thus, bevacizumab plus paclitaxel were discontinued and the treatment was changed to oral letrozole (2.5 mg/day). The patient has been followed up with no recurrence as of March 2013.

**Key Words** : breast cancer, bevacizumab

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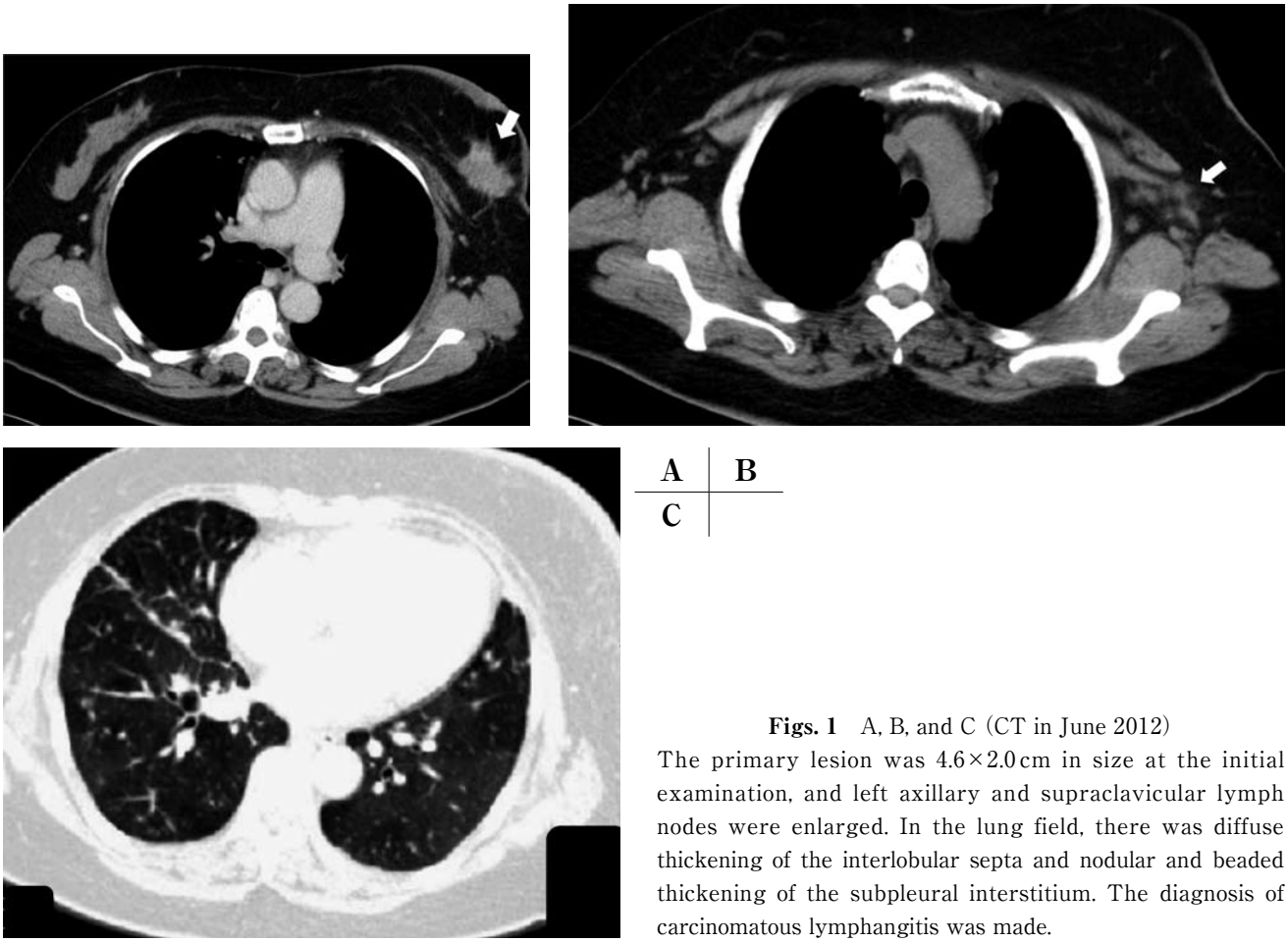
## INTRODUCTION

It is often difficult to cure metastatic breast cancer and recurrent breast cancer, except for some local recurrences. Thus, the objectives of treatment are im-




**Figs. 1** A, B, and C (CT in June 2012)
The primary lesion was 4.6×2.0 cm in size at the initial examination, and left axillary and supraclavicular lymph nodes were enlarged. In the lung field, there was diffuse thickening of the interlobular septa and nodular and beaded thickening of the subpleural interstitium. The diagnosis of carcinomatous lymphangitis was made.

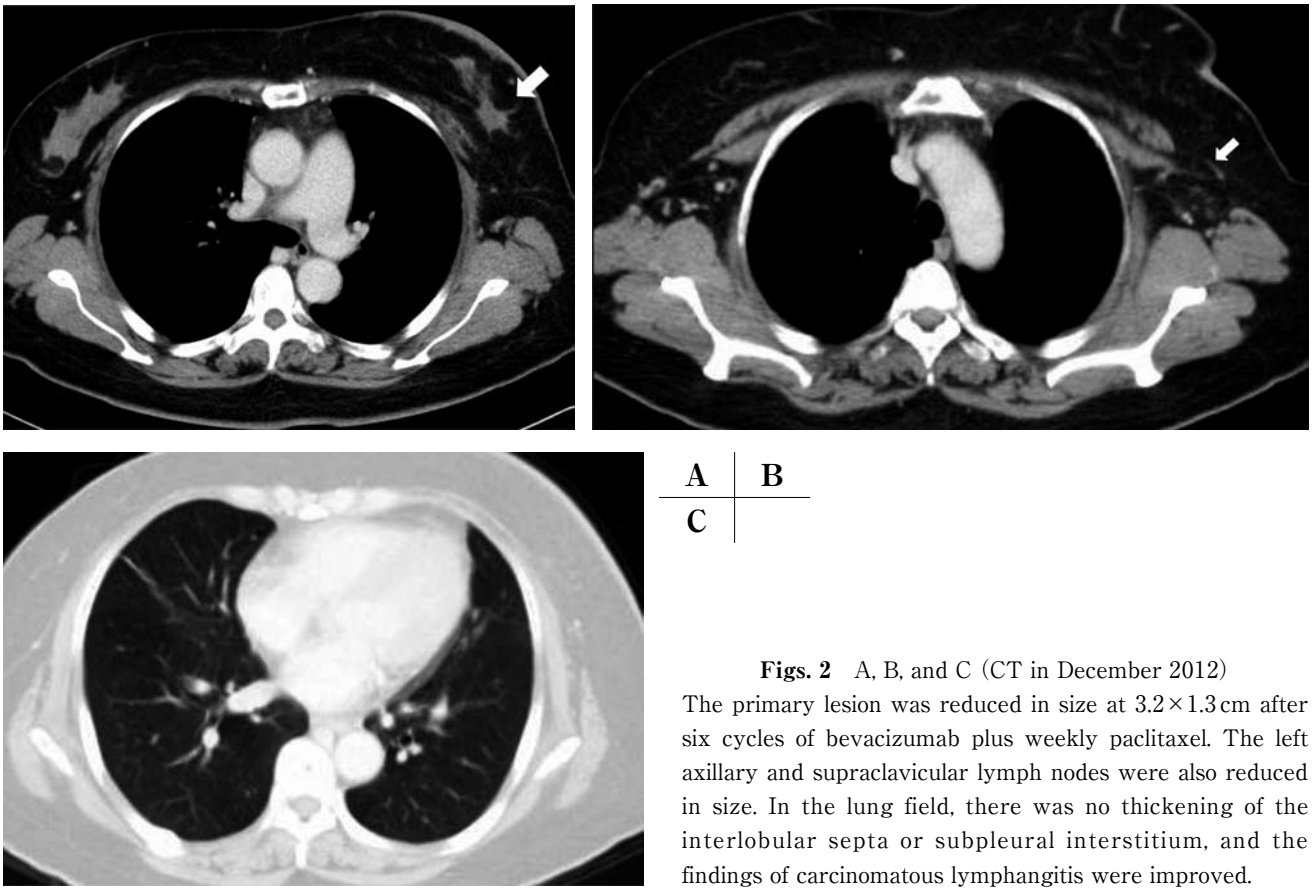
provement of QOL and extension of survival as for metastatic breast cancer and recurrent breast cancer. Carcinomatous lymphangitis is a life-threatening condition. When breast cancer patients also have carcinomatous lymphangitis, prognosis is very poor if good therapeutic effect is not achieved.

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), a major regulator involved in angiogenesis. In Japan, its indications are colon cancer and lung cancer and have been expanded to include breast cancer in September 2011. Addition of bevacizumab to paclitaxel therapy has been shown to significantly extend disease-free survival. However, the bevacizumab addition has not affected overall survival[1,2,3]. Thus, there is still controversy on the type of patients in whom bevacizumab should be used.

This report describes a case of advanced breast cancer and carcinomatous lymphangitis treated with bevacizumab plus paclitaxel. A positive therapeutic response was achieved and the therapy was subsequently changed to hormone therapy.

## CASE REPORT

The patient was a 53-year-old postmenopausal woman with a non-contributory medical history. She presented to a nearby hospital with chief complaints of continued exertional dyspnea and coughing since March 2012. Physical findings included a palpable mass in the left breast, and the patient was referred and presented to our hospital in May. In the physical examination, an elastic, hard mass of 5 cm in size was palpated in the left superior-lateral breast. At the same location, mammography revealed a high-density mass with spicules. Needle biopsy revealed infiltrating ductal carcinoma. The biopsy specimen showed a Ki-67 labeling index of 50% and was estrogen receptor positive, progesterone receptor positive, and without amplification of the human epidermal growth factor receptor 2 by FISH.




**Figs. 2** A, B, and C (CT in December 2012)
The primary lesion was reduced in size at 3.2×1.3 cm after six cycles of bevacizumab plus weekly paclitaxel. The left axillary and supraclavicular lymph nodes were also reduced in size. In the lung field, there was no thickening of the interlobular septa or subpleural interstitium, and the findings of carcinomatous lymphangitis were improved.

CT scans revealed a primary lesion of 4.6×2.0 cm in size, and enlargement of the left axillary lymph nodes and supraclavicular lymph nodes. In the lung field, there was diffuse thickening of the interlobular septa and nodular and beaded thickening of the subpleural interstitium. The diagnosis of carcinomatous lymphangitis was made (Figs. 1A, B, and C). Bone scintigraphy showed uptake in the spine, ribs, pelvis, and left femur (cT2N3cM1-stage IV). The condition was determined to be life threatening because there was carcinomatous lymphangitis with coughing and dyspnea. In June, administration of bevacizumab plus weekly paclitaxel (PTX) (PTX : 90 mg/m$^2$, 3 weeks on and 1 week off and bevacizumab : 10 mg/kg, every 2 weeks) was begun with the expectation of a high response rate. In addition, administration of zoledronic acid hydrate (4 mg/day, every 4 weeks) was begun for bone metastases. Coughing and dyspnea were resolved two weeks after beginning bevacizumab and paclitaxel administration. CT scans were taken in August after the completion of 3 cycles and showed improvement in carcinomatous lymphangitis. No major side effects were observed due to bevacizumab plus weekly paclitaxel. When the CT scans were taken in December after the completion of 6 cycles, the primary lesion and lymph node metastases were reduced in size. In the lung field, there was no thickening of the interlobular septa or subpleural interstitium, and the findings of carcinomatous lymphangitis were improved. Thus, the patient was determined to have a PR per the RECIST criteria (Figs. 2A, B, and C). The tumor marker levels decreased after initiation of bevacizumab plus weekly paclitaxel. The levels normalized after the completion of 4 cycles (Fig. 3).

The life-threatening condition had improved and the disease was stabilized. Thus, bevacizumab plus paclitaxel were discontinued and the treatment was changed to oral letrozole (2.5 mg/day). Thereafter the patient has been followed up without clinical exacerbation as of March 2013.

## DISCUSSION

Tumor growth requires oxygen and nutrients. Tumor vessels are needed to supply sufficient oxygen

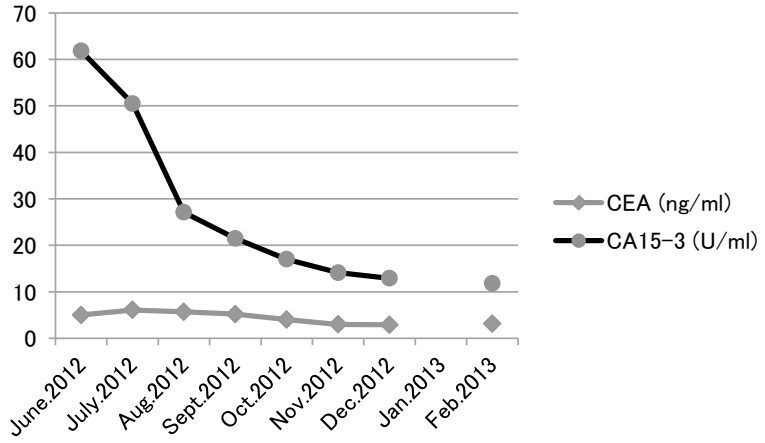



**Fig.3**
The tumor marker levels decreased after initiation of bevacizumab plus weekly paclitaxel. The levels normalized after the completion of 4 cycles.

and nutrients as the tumor size increases. Therefore, angiogenesis plays an important role in tumor growth and metastasis. VEGF is a major regulator involved in tumor angiogenesis, growth, and metastasis. It acts as a ligand and binds to VEGF receptors on the endothelial cell surface[4~6].

The molecularly-targeted drug bevacizumab (Avastin ; Genentech, South San Francisco, CA) selectively binds to a VEGF family member, VEGF-A. Bevacizumab inhibits binding of VEGF-A to VEGF receptors (VEGFR-1, VEGFR-2, and neuropilin 1) expressed on endothelial cells, thereby blocking the signal transduction pathway. It inhibits angiogenesis in tumor tissue and suppresses tumor growth as a result[7]. In addition, it has been shown to normalize the vascular structure, decrease vascular permeability, and lower increased tumor interstitial pressure[8,9]. When the tumor interstitial pressure is reduced by bevacizumab, paclitaxel delivery to the tumor tissue is improved. Thus, the drug concentration increases in the tumor tissue[10].

In 2007, there was a report on a phase III randomized trial (E2100) which compared paclitaxel plus bevacizumab and paclitaxel alone as initial chemotherapy for patients with untreated advanced and recurrent breast cancer (n=722). The overall survival was not significantly prolonged (median : 26.7 months vs 25.2 months, respectively, HR : 0.88, p=0.16). However, the median progression-free survival was prolonged (11.8 months vs 5.9 months, HR : 0.60, p<0.001) and the response rate increased (36.9% vs 21.2%, p< 0.001)[1]. In the U.S., bevacizumab was promptly approved for metastatic breast cancer in February 2008 based on these results. In Japan, its indications were expanded to include breast cancer patients in September 2011.

When additional trials were conducted (AVADO and RIBBON-1 trials), the results showed that the progression-free survival was prolonged and the response rate increased. However, the overall survival was not prolonged. In addition, the results suggested that the risks for adverse events could outweigh the benefits[2,3]. In November 2011, the Food and Drug Administration (FDA) revoked the approval of bevacizumab for breast cancer. Currently, there is still controversy on the type of patients in whom bevacizumab should be used, and it is necessary to thoroughly examine the risks and benefits before its use.

Carcinomatous lymphangitis is a form of lung metastasis from malignant tumor. It is a condition in which embolism of cancer cells occurs due to their infiltration into the intrapulmonary lymphatic vessels. The prognosis is poor, with less than half the patients surviving past 3 months of the first respiratory symptoms[11,12]. In recent years, patients with long term survival have been reported with advancement in treatment. Although not breast cancer cases, there have been reported cases of carcinomatous lymphangitis secondary to colorectal cancer in which long-term survival of 16 months was achieved using bevacizumab plus mFOLFOX6 as the initial treatment[13].

The patient of the present report had symptomatic carcinomatous lymphangitis. The condition was life threatening. Administration of bevacizumab plus weekly paclitaxel was initiated, and the patient achieved a positive therapeutic response. Thus, the treatment was changed to hormone therapy. High response rates can be obtained when bevacizumab is used in combination with another chemotherapeutic agent. Thus, bevacizumab is currently considered a drug with major benefits, particularly in patients with life-threatening metastasis as in the patient of this report.

In Japan, it has not been very long since bevacizumab has been indicated for metastatic and recurrent breast cancer. Since it has not been shown to prolong survival, its blind use is also not recommended from the aspect of health economics[14]. However, bevacizumab has been shown to achieve a high response rate and to prolong progression-free survival. Thus, it could be very beneficial depending on the case.

## CONCLUSION

We presented a case of advanced, life-threatening breast cancer with carcinomatous lymphangitis treated with bevacizumab plus paclitaxel. A positive therapeutic response was achieved and the therapy was subsequently changed to hormone therapy. In the future, more cases need to be accumulated to identify a subset of advanced and recurrent cancer patients in which bevacizumab will be more effective.

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