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CASE REPORT

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Severe thrombocytopenia and anemia as an initial presentation of breast cancer: A case report

Ryota Otsubo[1,2] | **Hiroshi Yano**[2] | **Hidehiro Itonaga**[3] | **Keisuke Iwasaki**[4] | **Keiko Segawa**[5] | **Takeshi Nagayasu**[1]

[1]Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

[2]Department of Breast Surgery, Sasebo City General Hospital, Nagasaki, Japan

[3]Department of Hematology, Sasebo City General Hospital, Nagasaki, Japan

[4]Department of Pathology, Sasebo City General Hospital, Nagasaki, Japan

[5]Department of Radiology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Correspondence
Ryota Otsubo, Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
Email: rotsubo@nagasaki-u.ac.jp

Abstract

Breast cancer patients with bone marrow metastasis (BMM) having profound thrombocytopenia and anemia are rare and there is no definitive treatment guideline. We present a case of successful initial treatment with anti-disseminated intravascular coagulation therapy and endocrine therapy, followed by chemotherapy to avoid deterioration of severe thrombocytopenia and anemia.

KEYWORDS

anemia, bone marrow metastasis, breast cancer, chemotherapy, endocrine therapy, thrombocytopenia

1 | INTRODUCTION

Breast cancer is the most common cancer among women globally.[1] Although the majority of patients with breast cancer are diagnosed at an early stage, metastatic breast cancer (MBC) is challenging to cure. Post-surgery recurrence occurs in approximately 20% of patients with operable breast cancer, while 70% of patients develop distant metastases.[2,3] Skeletal metastasis, which frequently affects patients with breast cancer, causes skeletal pain, pathological fractures, spinal cord compression, and hypercalcemia.[4] Bone marrow metastasis (BMM) has also been reported among patients with MBC. Cancer cells were detected in the bone marrow aspirates of approximately 30%–60% of patients with MBC.[5] However, patients with breast cancer rarely present with BMM and pronounced thrombocytopenia at the time of diagnosis.[6,7] Thus, the prognosis is bleak.[5,8] Chemotherapy is not recommended in patients with severe thrombocytopenia because of the risk of increased myelotoxicity and bleeding. We report a rare case of a patient with MBC, BMM, significant thrombocytopenia, and anemia treated with endocrine therapy, followed by chemotherapy.

2 | CASE PRESENTATION

A 55-year-old Japanese woman, who complained of progressive fatigue and lumbago, was hospitalized at Sasebo City General Hospital for severe thrombocytopenia and anemia. Her medical history was unremarkable, and she had no family history of breast cancer. On physical

examination, she had pale conjunctiva and experienced mild nasal bleeding, which could be controlled by compression. A palpable nodule, 3 cm in diameter, with no dermal changes, was noted on the inferomedial quadrant of her left breast. Her peripheral blood examination revealed a white blood cell count of 12,000/μL with 2% myeloblast, a hemoglobin level of 5.0 g/dL with high immature reticulocyte fraction (24.9%), and a platelet count of 18,000/μL with high immature platelet fraction (7.5%). She had a fibrin/fibrinogen degradation product level of 84.4 μg/mL (reference range, <5 μg/mL), fibrinogen level of 165 mg/dL (reference range, 180–320 mg/dL), and prothrombin time–international normalized ratio of 1.15. The patient was diagnosed with disseminated intravascular coagulation (DIC), based on the modified diagnostic criteria established by the Japanese Ministry of Health, Labor and Welfare.[9] She also had a CEA level of 282.0 ng/mL and CA15-3 level of 320 U/mL. A computed tomography examination of her chest revealed an enlarged left axillary lymph node and a nodular lesion in the medial region of the left breast. Computed tomography also revealed diffuse skeletal metastasis, involving multiple vertebrae (Figure 1) and pelvis. Mammography revealed an irregular spiculated mass in the inferomedial quadrant of the left breast (Figure 2), and breast ultrasound revealed an irregular, hypoechoic mass with a halo. A core-needle

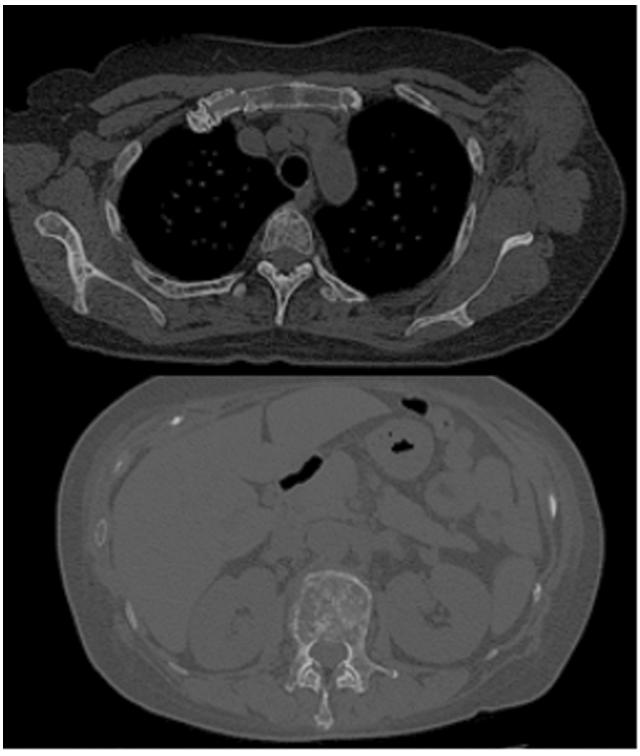

FIGURE 1 Computed tomography. Diffuse skeletal metastases involving multiple vertebrae were observed in the computed tomography of bone conditions

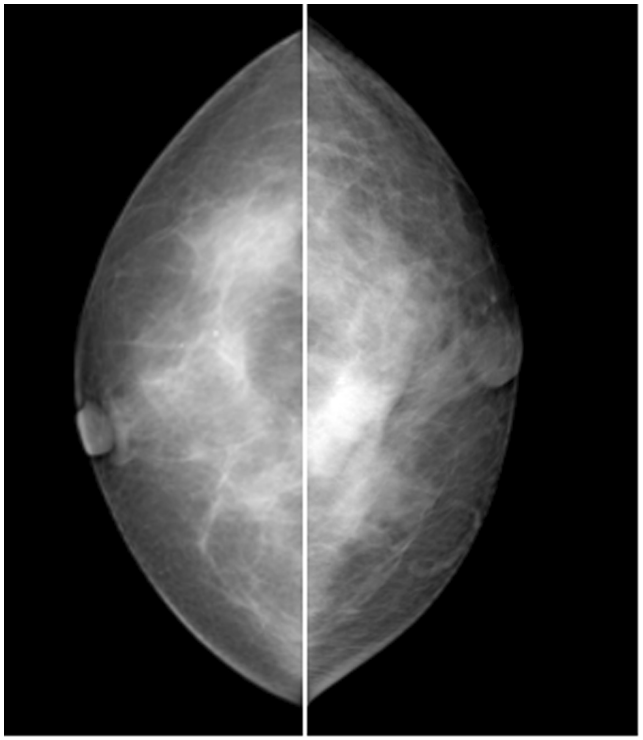

FIGURE 2 Mammography. An irregular spiculated mass in the medial side of the left breast was seen in the craniocaudal view of the mammography

biopsy of the left breast mass showed invasive ductal carcinoma, of nuclear grade 1, that was strongly positive for estrogen receptor (ER) and progesterone receptors (PgR), but negative for human epithelial growth factor receptor 2 (HER2) by immunohistochemical staining (Figure 3) and in situ hybridization, and 32.8% in Ki67 labeling index.

The patient's severe thrombocytopenia and anemia were further evaluated using a bone marrow biopsy. Frequent transfusions of packed red blood cells (pRBCs) and platelets were required. Clusters of abnormal cells were observed in the bone marrow specimen with the same features in immunohistochemical staining as those of the left breast mass (Figure 4). This strongly suggested BMM secondary to breast cancer, stage T2N1M1.

The risks and benefits of the treatment were evaluated since the patient had severe thrombocytopenia, anemia, and a tendency to bleed. She received recombinant human-soluble thrombomodulin (rhTM, 21,760 units per day, for 4 days) as anti-DIC therapy, denosumab (120 mg, every 4 weeks) as a bone-modifying agent for multiple bone metastasis and hypercalcemia (her corrected calcium value was 11.4 mg/dL), and systematic endocrine therapy with letrozole (2.5 mg per day). The patient's platelet count and hemoglobin gradually increased. Her fibrin/fibrinogen degradation product levels decreased, following frequent transfusions of pRBCs and platelets. The interval between transfusions gradually increased, and the patient was

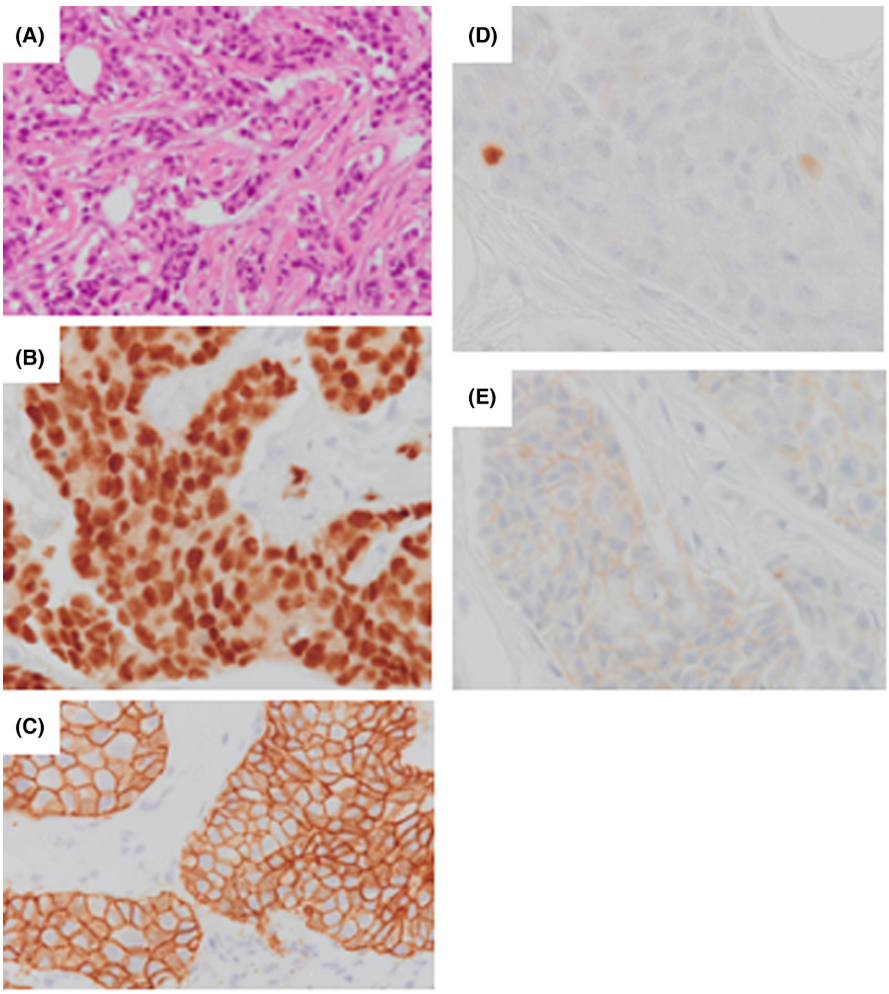

FIGURE 3 Core-needle biopsy of the left breast mass. A hematoxylin–eosin staining showed atypical epithelium with poor lumen formation in the fibrous stroma, and focal and cord-like branching infiltrates (A). Immunohistochemical staining showed strong staining for ER (B), E-cadherin (C), and weak staining for PgR (D) and HER2 (E)

discharged 51 days post admission with no bleeding tendency (Figure 5). Her corrected calcium value decreased to 8.9 mg/dL at the time of discharge and remained within the reference range from then on. She had an obvious decrease of tumor markers at the first outpatient visit after discharge, with a CEA level of 163.5 ng/mL and CA15-3 level of 278 U/mL. We changed the endocrine therapy from letrozole (2.5 mg) to fulvestrant (500 mg, every 4 weeks) after discharge, and blood transfusions gradually became unnecessary. The patient only required two pRBC transfusions post-discharge. She developed multiple liver metastases 4 months post-discharge. She was treated with paclitaxel (100 mg) and bevacizumab (550 mg) once in 2 weeks for 6 months. The patient died of liver failure due to progressive liver metastases 13 months after the initial diagnosis.

3 | DISCUSSION

There have been few reports on patients with MBC with symptomatic BMM. Anemia was the most common symptom, with 40%–60% of patients with BMM having a hemoglobin level of less than 12 g/dL.[6] Thrombocytopenia, leukocytopenia, or both have been reported in only 12%–25% of patients with aberrant bone marrow results.[6] A multivariate analysis of the prognostic markers in patients with MBC revealed that a pretreatment hemoglobin level of <11 g/dL and a platelet count of <100,000/μL negatively influenced prognosis. A low baseline physical status, along with the combination of bone and visceral metastases, negatively affect the prognosis.[10] In the present case, endocrine therapy was effective as an initial treatment for severe thrombocytopenia and anemia secondary to BMM. However, the patient developed liver metastases 5 months later; therefore, treatment was discontinued. It was replaced with chemotherapy, consisting of paclitaxel and bevacizumab.

DIC that exists at the diagnosis or occurs during cancer therapy prevents continuation of therapy and results in a poor prognosis. The cornerstone of treatment for DIC in cancer patients includes anti-cancer treatment, anticoagulant treatment, replacement therapy such as blood transfusion and natural protease inhibitor, and systemic control.[11] Indeed, the evidence for rhTM therapy in DIC

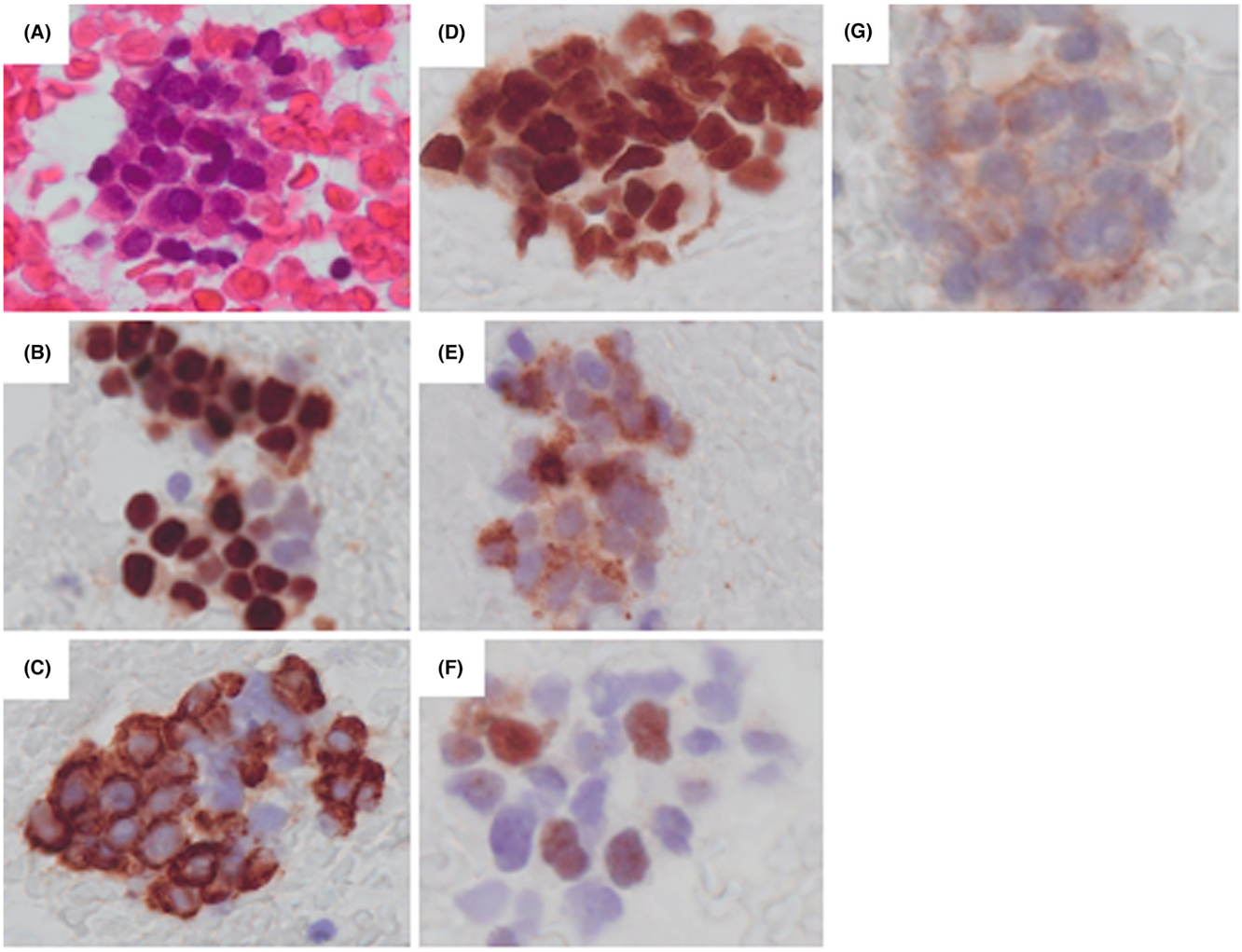

FIGURE 4 Bone marrow biopsy specimen. Small clusters of abnormal cells with enlarged nuclei were observed in the bone marrow biopsy specimen (A; hematoxylin–eosin). Immunohistochemical staining revealed strong staining for ER (B), E1/AE3 (C), GATA3 (D), and mammaglobin (E), and moderate staining for PgR (F) and HER2 (G)

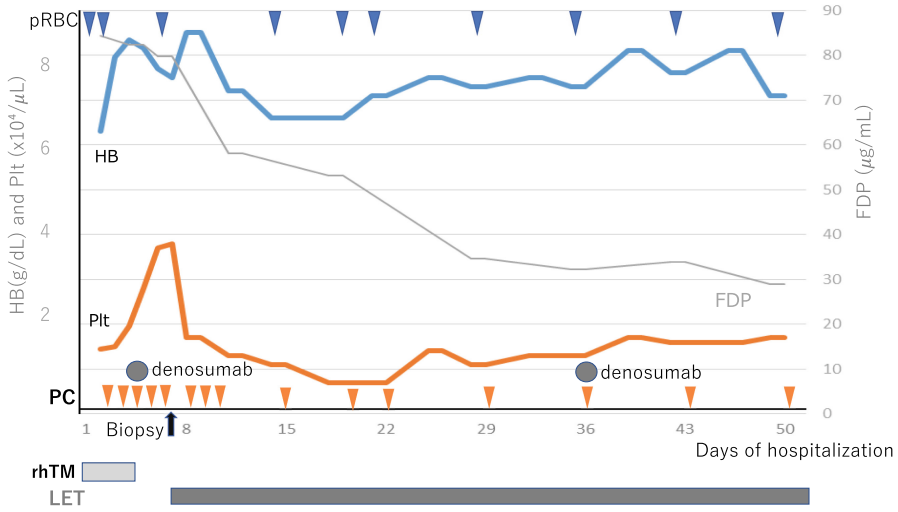

FIGURE 5 Clinical course of the patient. The patient's platelet, hemoglobin, and fibrin/fibrinogen degradation products levels showed hematopoietic recovery. Decreasing numbers of transfusions of packed red blood cells and platelet concentrates were needed after endocrine therapy with letrozole. FDP, fibrin/fibrinogen degradation products; HB, hemoglobin; LET, letrozole; PC, platelet concentrates; Plt, platelet; pRBCs, packed red blood cells; rhTM, recombinant human-soluble thrombomodulin

due to sepsis and hematological disease is found in several reports[12–14] but that in solid tumor-related DIC is rare. A retrospective study revealed that rhTM therapy for solid tumor-related DIC improved DIC score and DIC-related blood test data. Additionally, longer overall survival (178 days in median) was seen in patients who were treated with chemotherapy than without chemotherapy (17 days in median).[15] There is a novelty in the successful initial endocrine therapy, for severe thrombocytopenia and anemia, followed by chemotherapy in our case. Although patients with breast cancer were a minority in the analysis of three previous reports, rhTM therapy is considered as one of the therapy options in patients with solid tumors.[11] The efficacy of weekly systemic low-dose chemotherapy utilizing anthracycline derivatives, concurrent endocrine treatment, and bisphosphonates was demonstrated in five patients with breast cancer with BMM and severe thrombocytopenia at the time of diagnosis.[16] The efficacy of the treatment with low-dose capecitabine has also been reported in five patients with BMM and platelet counts ranging from 70,000 to 80,000/μL.[17] In a single-institution review, 20 of the 22 patients with BMM received various chemotherapies, but none of them had BMM during the initial diagnosis of breast cancer.[18] A previous report featured a patient with primary MBC with BMM and pronounced thrombocytopenia at the time of diagnosis of breast cancer. The patient was initially treated with tamoxifen, but there was no response. Therefore, standard-dose cytotoxic therapy was initiated.[19] Letrozole was initiated for a patient with occult breast cancer, whose bone marrow biopsy showed ER-positive malignant cells with anemia and thrombocytopenia, because administration of chemotherapy was judged risky for fatal bleeding due to low platelet count. After initial endocrine therapy, anemia and thrombocytopenia gradually improved and the endocrine therapy was continued for 2 years until the deterioration of bicytopenia.[20] In the present case, the patient was also responsive to the initial aromatase inhibitor, resulting in the resolution of thrombocytopenia and anemia. Cyclin-dependent kinase (CDK) 4/6 inhibitors were not available during the patient's treatment period. A recent report showed that letrozole and leuprorelin plus the CDK 4/6 inhibitor palbociclib was effective for a young woman with ER-positive HER2-negative MBC with pancytopenia owing to carcinomatosis of the bone marrow, and she remained in complete remission for 26 months with this treatment regimen.[21]

We reported a rare case of a woman presenting with BMM, severe thrombocytopenia, and anemia when she was initially diagnosed with breast cancer. This case shows that endocrine therapy, followed by chemotherapy, can be a viable treatment option for patients with BMM-associated pronounced thrombocytopenia and bleeding episodes.

AUTHOR CONTRIBUTIONS

Ryota Otsubo: Conceptualization; investigation; methodology; project administration; resources; validation; visualization; writing – original draft; writing – review and editing. **Hiroshi yano:** Resources; supervision; writing – review and editing. **Hidehiro Itonaga:** Resources; supervision; writing – review and editing. **Keisuke Iwasaki:** Resources; visualization; writing – review and editing. **Keiko Segawa:** Resources; visualization; writing – review and editing. **Takeshi Nagayasu:** Conceptualization; supervision; writing – review and editing.

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CONFLICT OF INTEREST

All authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICAL APPROVAL

This case report has been granted an exemption from requiring ethics approval of the ethics committee in Sasebo City General Hospital because we obtained written informed consent from the patient's husband after her death and the report contains nothing which might be considered a risk to the patient privacy.

CONSENT

Written informed consent was obtained from the patient's next of kin for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

We do not need any permission to use any material in this report since the materials used are original.

ORCID

Ryota Otsubo https://orcid.org/0000-0003-3084-2164

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