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Case Report

Intravenous Immunoglobulin to Suppress Progression in a Patient With Advanced Breast Cancer

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Conflict of Interest
The authors declare that they have no competing interests.

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ABSTRACT

Intravenous immunoglobulin (IVIG) is used to treat various diseases and has anticancer effects that suppress metastases in animal models of sarcoma and melanoma. However, these effects have been observed in a limited number of clinical cases. We report the case of a patient with metastatic breast cancer in which long-term IVIG treatment stopped disease progression in the absence of salvage chemotherapy. The patient was treated with IVIG for the treatment of immune thrombocytopenia. Surprisingly, the lung and brain metastases were stabilized, and the patient achieved a progression-free interval of 29 months. More cases are needed to investigate and confirm the efficacy of IVIG in solid tumors in the future.

Keywords: Carcinoma, Ductal, Breast; Immunoglobulins, Intravenous; Purpura, Thrombocytopenic, Idiopathic

INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by isolated thrombocytopenia [1]. ITP results in autoantibody-mediated destruction of platelets in the spleen. Intravenous immunoglobulin (IVIG) is derived from donor plasma and contains purified immunoglobulin G (IgG). IVIG is used to treat various diseases, including immunodeficiency, as well as autoimmune, systemic inflammatory, and neurodegenerative disorders [2]. IVIG exhibits anticancer effects that suppress metastases in several animal models [3,4]. However, these effects were observed in a limited number of patients, including a case report and a clinical study of metastatic melanoma [5,6] and a case report of soft tissue sarcoma [7]. Here, we report that long-term IVIG treatment stopped disease progression in a patient with advanced breast cancer with lung and brain metastases in the absence of salvage breast cancer therapy.

CASE REPORT

A 43-year-old woman was diagnosed with Sjogren syndrome with dryness of the eyes and mouth since 2006. In April 2016, she was diagnosed with invasive ductal breast carcinoma

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(pT1N0M0, stage I; **Figure 1**). **Figure 2** summarizes the entire clinical course, treatment, and response of the patient. Immunohistochemical tests for estrogen receptor, progesterone receptor, and human epithelial growth factor receptor were negative. She underwent breast conservation surgery and adjuvant chemotherapy with cyclophosphamide, epirubicin, and fluorouracil. She received three cycles of chemotherapy, and thrombocytopenia developed after the second cycle of adjuvant chemotherapy. Thrombocytopenia (platelet count,16,000/μL) persisted and became refractory to platelet transfusion after the third cycle of adjuvant chemotherapy. In addition, the patient had severe menorrhagia. As a result, adjuvant chemotherapy was discontinued, and chemotherapy-induced thrombocytopenia was suspected. However, the platelet count did not recover to baseline during the 6-month follow-up. Bone marrow biopsy and all pertinent laboratory studies were normal except for a positive antiplatelet antibody test; therefore, a clinical diagnosis of ITP was established. Eltrombopag (25 mg daily), hydroxychloroquine, prednisolone, mycophenolate mofetil, and danazol were administered, but the response was limited. Splenectomy was not considered because of the high risk of bleeding. Subsequently, she did not receive any cancer treatment.

The patient developed lung metastases with a diameter of 1 cm in the right lower lobe (**Figure 3**) and tiny subpleural nodules in the right middle lobe 28 months after the operation. Six months later, the patient suffered from severe vertigo, headache, and vomiting. Magnetic resonance

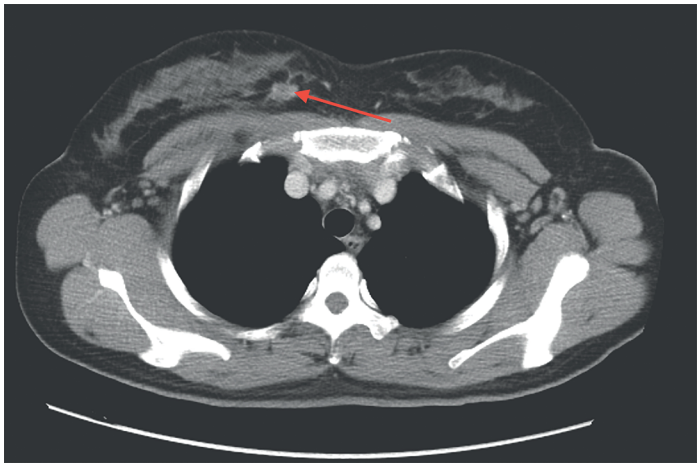

Figure 1. Contrast-enhanced chest CT imaging. Contrast-enhanced chest CT imaging before breast conservation surgery indicated a 1.4-cm diameter heterogeneous mass in the upper inner quadrant of the right breast (red arrow). No enlarged lymph nodes were observed in the bilateral subaxillary, hilar, or mediastinal regions.
CT = computed tomography.

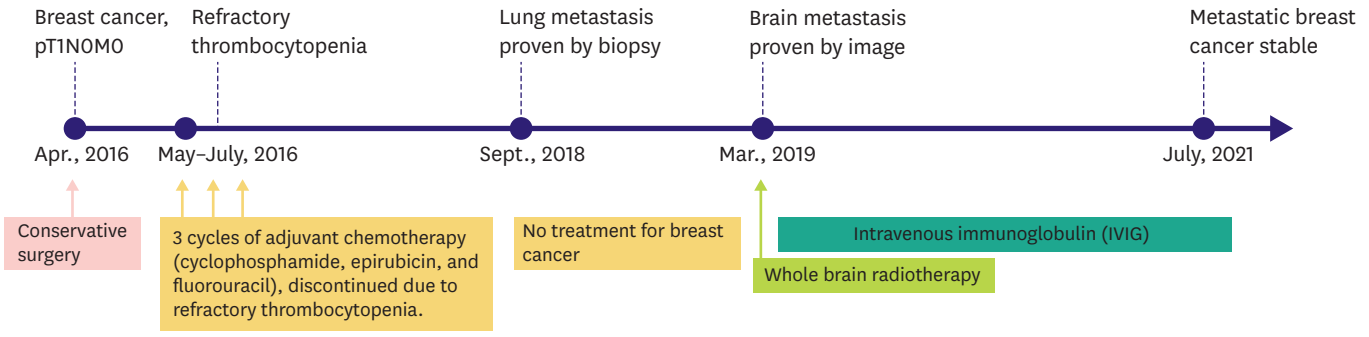

Figure 2. Summary of the clinical course, overall treatment administered, and treatment response.

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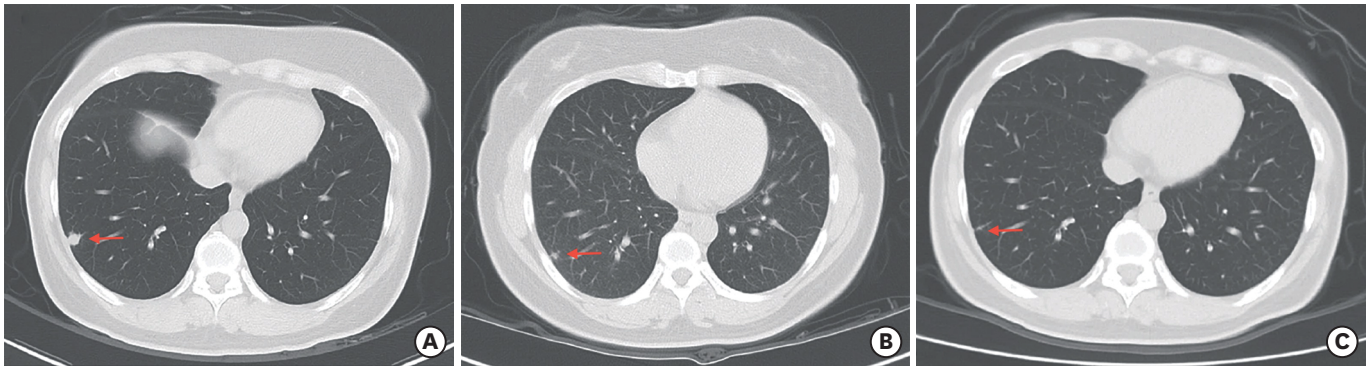

Figure 3. Serial noncontrast-enhanced axial chest computed tomography imaging at the level of T8–T9. (A) A new 1-cm diameter, irregular nodular opacity along the pleural surface of the right upper lobe occurred 26 months after the last course of chemotherapy; (B) the nodule was reduced to 0.4 cm in diameter 6 months after IVIG therapy; (C) no significant interval change 24 months after IVIG therapy. The red arrows indicated the metastatic lung lesions.
IVIG = intravenous immunoglobulin.

imaging of the brain revealed multiple enhancing lesions in the bilateral cerebral and cerebellar hemispheres, with the largest measuring 2.3 cm (**Figure 4**). Brain metastases were confirmed radiologically. Whole-brain radiotherapy was administered (14 fractions of 3500 mGy) in March 2019. The sizes of the brain metastases were all regressed (with the largest size of approximately 1.3 cm) (**Figure 4B**). For refractory ITP and a high risk of bleeding, the patient began to receive IVIGs at a dosage of 0.4 g/kg/day for 3 consecutive days every 3 weeks. Her platelet count recovered to approximately 100,000/μL in subsequent cycles of IVIG therapy. Notably, the lung metastases slightly decreased half a year after the initiation of IVIG (all of them less than 1 cm) (**Figure 3**). Moreover, in further repeated imaging studies, metastatic breast cancer in the brain and lungs remained stable without new metastatic lesions for 29 months (**Figures 3** and **4**). No side effects from IVIG therapy were reported, and the patient maintained a normal life. During the course, the patient did not receive palliative chemotherapy or targeted therapy for breast cancer.

DISCUSSION

Of all subtypes of breast cancer, triple-negative breast cancer has the worst prognosis and the highest likelihood of recurrence. Published data suggest that metastatic triple-negative breast cancer has a median survival of approximately 1 year [8] and a 5-year survival rate of 12% [9]. This is the first known case of sustained tumor stabilization from IVIG treatment alone in an advanced triple-negative breast cancer patient with lung and brain metastases. Without any anticancer therapy, IVIG treatment suppressed the progression of breast cancer and metastases in the lungs and brain. This therapy provided a prolonged progression-free survival time of at least 29 months in our patient with metastatic triple-negative breast cancer. This extraordinary outcome suggests that IVIG may be an alternative therapy for breast cancer.

Clinical experience with IVIG for patients with cancer is scarce, but beneficial antimetastatic effects have been described in several animal studies [5-7,10]. In mouse models of melanoma and sarcoma, the administration of IVIG significantly inhibited cancer progression and prolonged survival [10]. A similar effect was reported in a mouse model of sarcoma [7]. Recently, Xu et al. [11] demonstrated that low-dose IgG might induce macrophage polarization toward the M1 profile, and it was effective in suppressing tumor progression in mouse models of three cancer types (melanoma, breast cancer, and colon cancer).

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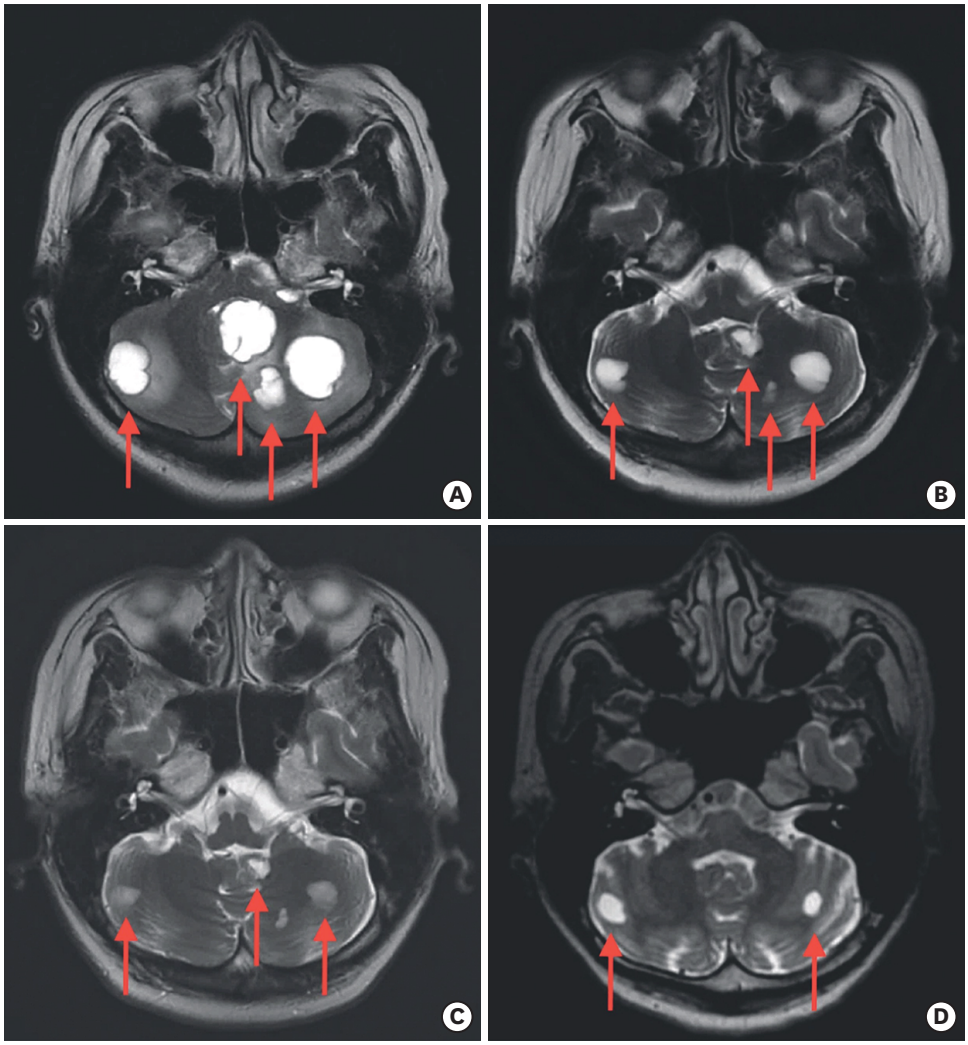

Figure 4. Axial T2-weighted MR image at the pons level. (A) Pre-radiosurgical MR image before IVIG therapy and WBRT; (B) 2 months after IVIG therapy and WBRT; (C) 7 months after IVIG therapy and WBRT indicated the larger metastatic lesions in the bilateral cerebellar hemispheres exhibited regression in size; (D) 28 months after IVIG therapy and WBRT indicated no interval change. The red arrows indicated the metastatic brain lesions.
MR = magnetic resonance; IVIG = intravenous immunoglobulin; WBRT = whole brain radiotherapy.

The antimetastatic effects and safety of IVIG have been reported. In one case report, a patient with malignant peripheral nerve sheath tumor received IVIG (0.4 g/kg) once every 6 weeks for multiple sclerosis and had a stable disease status for 30 months [7]. In another case report, a patient with metastatic melanoma receiving high-dose IVIG (2 g/kg) experienced liver metastasis regression and stabilization of lung metastases for 9 months [5]. In a third report, nine patients with metastatic melanoma who failed prior chemotherapy and immunotherapy were treated with IVIG therapy (1 g/kg) every 3 weeks [6]. Two of the patients achieved stable disease status for 3 and 8 months, respectively, but the metastases progressed thereafter. To our knowledge, no other clinical reports have illustrated the substantial antimetastatic effect of IVIG therapy on solid tumors. In our case, a patient with metastatic breast cancer receiving only IVIG therapy achieved stable disease status for more than 2 years. This indicates that IVIG therapy may improve the prognosis of patients with advanced-stage cancer and has great potential for metastatic solid tumor treatment.

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The mechanisms by which IVIG inhibits metastasis progression are multifactorial and not fully understood. IVIG may halt tumor progression by inducing tumor cell apoptosis [4,12]. IVIG was observed to enhance the apoptotic gene expression of p53, p21, and pRb in cancer cells and to inhibit cancer cell proliferation [3]. IVIG also induces interleukin-12 and transforming growth factor-β secretion, which potentiates natural killer cell activity and increases anticancer effects. Antiangiogenic effects and activity against tumor adhesion machinery have also been proposed [10]. IVIG protects the basement membrane and intercellular matrix integrity and prevents cell invasion by decreasing matrix metalloproteinase-9 mRNA expression and protein levels [7]. F(ab')2 fragments from IVIG have an affinity for binding to cancer cells and initiating antibody-dependent cell-mediated cytotoxicity [13]. Domínguez-Soto et al. observed that the dissemination of tumors depends on tumor-associated macrophages (M2), and IVIG could inhibit this process by modulating cytokines and inducing M2 (protumoral)-to-M1 (antitumoral) polarization [14].

The current study showed that IVIG treatment suppressed the progression of breast cancer and metastases in the lungs and brain without any anticancer therapy, except for whole-brain radiotherapy. Although whole-brain radiotherapy may have contributed to the progression of brain metastases, it is noteworthy that a previous study reported that the intracranial progression-free duration was 6 months (95% confidence interval [CI], 3.5–8.5 months) in patients with multiple brain metastases [15]. Furthermore, the median survival after a diagnosis of brain metastases in patients who received adjuvant radiation therapy was 3.6 months (95% CI, 1.5–8.9 months) [16]. In another retrospective study, the median survival for patients with brain metastases who received whole-brain radiotherapy was 4.2 months [17]. Consequently, the improved survival might not be entirely attributable to whole-brain radiotherapy. It is possible that both IVIG and whole-brain radiotherapy provided a synergistic or additive effect on the stabilization of brain metastases. The effect of IVIG therapy and radiation therapy on brain metastases should be considered in further long-term follow-up studies in patients with metastatic breast cancer.

In conclusion, we report the first case of metastatic breast cancer in the lungs and brain that was incidentally stabilized by IVIG treatment. The administration of IVIG may play a role in suppressing tumor progression and metastasis with few side effects in patients with solid tumors.

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