

Capillary Hemangioma of the Breast Parenchyma Mimicking New Primary Cancer or Metastasis During Ramucirumab Therapy for Advanced Gastric Cancer

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Abstract

Background/Aim: Ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor receptor-2 (VEGFR-2), has been shown to prolong survival in patients with advanced gastric cancer when combined with paclitaxel as second-line chemotherapy in the RAINBOW study. The most common adverse events include hypertension, proteinuria, and hemorrhage, reflecting its anti-angiogenic activity. Although the VEGF signaling pathway is strongly implicated in the pathogenesis of hemangiomas, the development of new hemangiomas during VEGFR-2 inhibition is rarely reported.

Case Report: A 38-year-old woman with stage IV gastric adenocarcinoma presented with peritoneal dissemination and lymph node metastasis. She initially received FOLFOX plus immune checkpoint inhibitor therapy, achieving a partial response before disease progression. Second-line treatment with paclitaxel and ramucirumab was initiated. During therapy, chest computed tomography revealed a newly developed contrast-enhancing nodule in the left breast parenchyma, raising suspicion of metastasis or primary breast carcinoma. Breast ultrasonography confirmed a hypervascular lesion, and ultrasound-guided biopsy demonstrated numerous capillary-sized vessels lined by bland endothelial cells, consistent with capillary hemangioma. Owing to deterioration of her general condition, chemotherapy was temporarily discontinued. Despite subsequent third-line FOLFIRI and fourth-line trifluridine/tipiracil treatment, the patient eventually died of disease progression. Notably, follow-up chest CT scans showed gradual reduction and eventual spontaneous disappearance of the breast hemangioma, independent of systemic therapy.

Conclusion: This is a rare case of a breast parenchymal capillary hemangioma arising during ramucirumab therapy for advanced gastric cancer, which regressed spontaneously. Clinicians should recognize that atypical vascular lesions may develop paradoxically during VEGFR-2 blockade and confirm histological diagnosis to avoid misinterpretation as metastasis or new primary malignancy.

Keywords: Capillary hemangioma, breast parenchyma, ramucirumab, VEGFR-2 inhibition, hypervascular lesion.

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Received September 12, 2025 | Revised October 10, 2025 | Accepted October 13, 2025



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Introduction

Ramucirumab is a fully human monoclonal antibody directed against vascular endothelial growth factor receptor-2 (VEGFR-2), thereby suppressing angiogenesis. Results from the pivotal RAINBOW trial demonstrated that the addition of ramucirumab to paclitaxel as a second-line regimen significantly improved overall survival in patients with advanced gastric cancer, leading to its incorporation as a standard therapeutic option (1-3). The predominant toxicities observed with ramucirumab include hypertension, proteinuria, and hemorrhagic events, all primarily related to its anti-angiogenic activity.

Interestingly, the VEGF signaling pathway is recognized as a critical mediator in the development of hemangiomas (4). For this reason, the appearance of new hemangiomas is considered an uncommon event during VEGFR-2 blockade with anti-angiogenic agents (5-7). Recent studies further refine second-line practice. The YCOG1601 trial demonstrated that paclitaxel plus ramucirumab is feasible even in older adults, with manageable toxicities (8). Moreover, a 2024 phase II study suggested that ramucirumab beyond progression after paclitaxel–ramucirumab may be a viable option for selected patients (9). These reports provide important context to our case, which highlights a paradoxical vascular lesion arising under VEGFR-2 inhibition.

In this report, we describe an unusual case of a capillary hemangioma arising within the parenchyma of the left breast during combined treatment with ramucirumab and paclitaxel for advanced gastric cancer. The lesion was initially misinterpreted as possible metastatic disease but was subsequently confirmed histologically as a hemangioma. Furthermore, potential biological mechanisms underlying this paradoxical finding are reviewed.

Case Report

A 38-year-old woman presented in December 2022 with complaints of abdominal distension and discomfort. Endoscopic evaluation with esophagogastroduodenoscopy,

along with abdominal computed tomography (CT), revealed advanced gastric carcinoma (stage IV) accompanied by peritoneal dissemination and preaortic lymph node involvement. Histopathological analysis confirmed poorly differentiated adenocarcinoma. Immunohistochemistry showed negative HER2 status but positive PD-L1 expression with a tumor proportion score $\geq 5\%$. Mismatch repair proteins were intact, and next-generation sequencing failed to identify any actionable mutations, indicating microsatellite stability.

The patient was initially treated with FOLFOX combined with nivolumab. After four cycles, a partial response was achieved and maintained across 13 cycles. Disease progression was later documented, with CT scans showing peritoneal thickening and omental caking. At this time, chest CT revealed no abnormalities, and the left breast appeared unremarkable (Figure 1A).

Second-line therapy with paclitaxel plus ramucirumab was initiated, resulting in symptomatic relief and radiographic shrinkage of peritoneal disease within two months. However, follow-up chest CT at that point detected a newly developed, contrast-enhancing nodule measuring approximately 1 cm beneath the left subareolar region, raising suspicion of metastatic disease or primary breast carcinoma. Although the lesion was not palpable, ultrasonography demonstrated a hypervascular pattern. Ultrasound-guided biopsy was subsequently performed.

Histological examination showed relatively well-demarcated borders with numerous capillary-sized vessels proliferating within fibrous stroma [Figure 2A, Hematoxylin and Eosin (H&E) stain $\times 200$]. The vessels were lined by a single layer of flattened or mildly hypertrophic endothelial cells without nuclear atypia or mitotic activity. High-power views confirmed vascular channels containing erythrocytes and endothelial cell positivity (Figure 2B, H&E $\times 400$), consistent with a capillary hemangioma.

Despite continuation of therapy, the patient discontinued chemotherapy for approximately two months due to worsening performance status. A

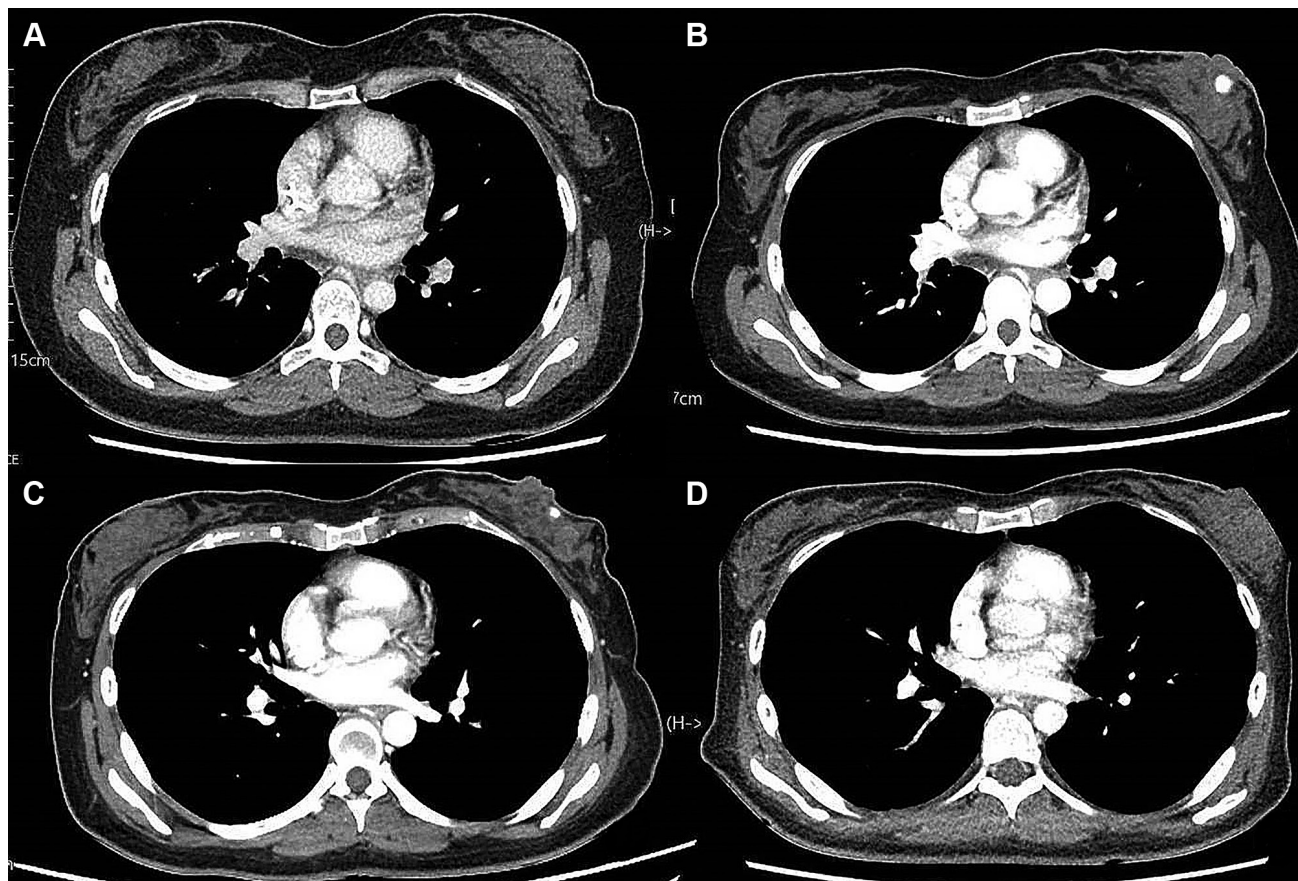


Figure 1. Chest computed tomography findings during treatment. (A) Chest computed tomography (CT) performed at the time of disease progression after first-line chemotherapy shows no remarkable findings in the left breast parenchyma. (B) A response evaluation CT after two cycles of second-line chemotherapy (paclitaxel plus ramucirumab) shows an enhanced nodule within the left breast parenchyma. (C) Follow-up CT performed two months after discontinuation of ramucirumab shows that the size of the hypervascular nodule has reduced. (D) Final chest CT obtained two months after (C) shows that the entire left breast could not be fully visualized; however, no hypervascular nodule can be identified in the visible portion.

subsequent CT demonstrated renewed progression of peritoneal disease but a slight reduction in the size of the breast lesion (Figure 1C). Third-line treatment with FOLFIRI was administered for three cycles, providing transient improvement in abdominal complaints before progression to massive ascites. Fourth-line therapy with trifluridine/tipiracil (Lonsurf) was attempted, but the patient ultimately succumbed to rapid disease progression. Notably, the final chest CT revealed complete disappearance of the previously noted breast nodule (Figure 1D).

Discussion

The RAINBOW trial established the combination of paclitaxel and ramucirumab as the global standard second-line therapy for advanced gastric cancer (1). Ramucirumab functions as a monoclonal antibody against VEGFR-2, thereby inhibiting angiogenesis and suppressing tumor progression and metastatic spread (2). Reported adverse events most frequently include hypertension, proteinuria, and bleeding complications (1, 3). In contrast, the appearance of hemangiomas during

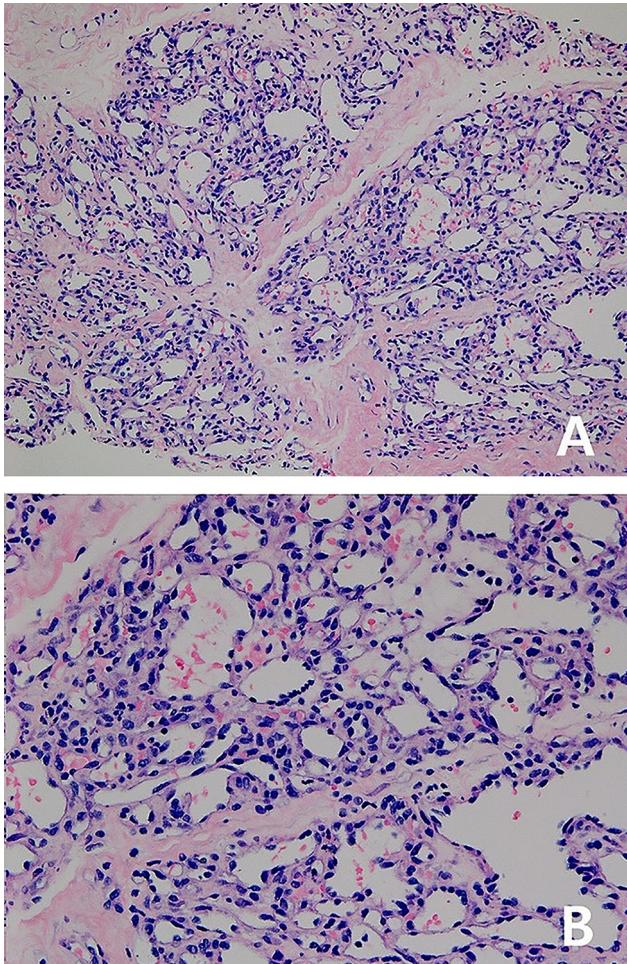


Figure 2. Pathological findings of the capillary hemangioma in the left breast. (A) Low-power view [Hematoxylin and Eosin (H&E) stain, $\times 200$] shows numerous capillary-sized vessels proliferating within a fibrous stroma. (B) High-power view (H&E stain, $\times 400$) demonstrates vascular channels lined by bland, single-layered endothelial cells containing red blood cells. No cytologic atypia, mitosis, necrosis, or infiltrative growth pattern can be observed.

ramucirumab treatment is extremely uncommon and was not prominently observed in large clinical trials (1-3). To our knowledge, the present case represents the first report of a breast parenchymal capillary hemangioma arising during paclitaxel–ramucirumab therapy for gastric cancer, posing diagnostic challenges in distinguishing it from metastatic or primary breast carcinoma.

Hemangiomas are benign vascular tumors characterized by endothelial cell proliferation. The VEGF

signaling pathway has been recognized as a central mediator in their pathogenesis (4). Thus, the occurrence of hemangiomas during VEGFR-2 blockade appears paradoxical. Nevertheless, isolated cases of cutaneous hemangiomas following anti-VEGF therapy have been documented (5). Moreover, a phase I study of tanibirumab, a VEGFR-2–targeting antibody, demonstrated hemangioma-like lesions in more than 60% of treated patients (6). These observations raise the possibility of a mechanistic link between VEGF pathway inhibition and aberrant vascular proliferation (6, 7).

The precise mechanisms underlying hemangioma development under VEGFR-2 suppression remain undefined. Several hypotheses have been proposed: (i) somatic mutations or functional alterations in the *KDR* (*VEGFR2*) gene may induce vascular malformations (10); (ii) VEGFR-2 blockade may alter vascular hemodynamics, favoring endothelial proliferation (11, 12); (iii) local hypoxia caused by reduced angiogenic signaling may activate the HIF-1 α pathway, leading to the upregulation of alternative proangiogenic mediators such as VEGF, fibroblast growth factor, and platelet-derived growth factor (13, 14); and (iv) VEGFR-2 inhibition may trigger abnormal intracellular signaling cascades, thereby contributing to atypical vascular responses (15, 16).

In summary, we describe the first case of a breast parenchymal capillary hemangioma occurring during ramucirumab therapy for gastric cancer, initially misdiagnosed as metastatic or primary breast cancer. This case highlights the clinical importance of recognizing atypical vascular lesions arising during antiangiogenic treatment. Awareness of this phenomenon may prevent unnecessary interventions, and histological confirmation should be emphasized whenever new vascular nodules are detected in patients receiving VEGFR-2 inhibitors. Importantly, recent clinical studies have broadened the understanding of ramucirumab use in diverse patient populations and beyond progression (8, 9, 17), yet paradoxical vascular lesions such as hemangiomas remain under-recognized and warrant further investigation (18, 19).

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

KHB and LYA contributed to the writing of the manuscript. PSG and KSH were involved in writing, editing and reviewing the manuscript. All Authors read and approved the final manuscript.

Funding

The present study was supported by grants from the Clinical Medicine Research Institute at Chosun University Hospital, 2023.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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