

Metastatic Invasive Lobular Breast Carcinoma Involving Tamoxifen-related Endometrial Polyp in a Patient With Metachronous Bilateral Breast Carcinomas: A Case Report

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Abstract

Background/Aim: Metastasis of extragenital malignancies to the female genital tract, particularly the uterus, is exceedingly rare. Invasive lobular carcinoma (ILC) is the most common histological type of breast carcinoma that metastasizes to gynecologic organs.

Case Report: A 42-year-old woman receiving tamoxifen presented with an irregularly thickened endometrium on transvaginal ultrasonography. She had previously undergone bilateral partial mastectomies – eight years prior for right-sided invasive ductal carcinoma, and three years prior for left-sided ILC. Hysteroscopic evaluation revealed an endometrial polyp. Microscopic examination of the polypectomy specimen showed variably sized, irregularly shaped branching glands embedded in densely fibrotic stroma. Within the stroma, monomorphic tumor cells with hyperchromatic, eccentrically located nuclei were arranged in single files, thin cords, or nests. Immunostaining revealed that the tumor cells were positive for GATA-binding protein 3 and negative for paired box 8, supporting a diagnosis of metastatic carcinoma from the breast. The final pathological diagnosis was metastatic ILC involving a tamoxifen-associated endometrial polyp.

Conclusion: Although rare, breast carcinoma may metastasize to endometrial polyps. Clinicians and pathologists should consider this possibility when evaluating abnormal ultrasonographic findings in the female genital tract, particularly in patients with a history of breast carcinoma receiving tamoxifen therapy. Abnormal ultrasonographic findings in the uterus of such patients warrant a comprehensive diagnostic workup to exclude metastatic disease.

Keywords: Breast, invasive lobular carcinoma, metastasis, endometrial polyp, tamoxifen.



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Introduction

Metastasis of extragenital malignancies to the female genital tract is an uncommon phenomenon (1-3). When it does occur, the ovaries are most frequently involved, accounting for approximately 80% of all cases (4). Uterine metastases are rare, comprising less than 10% of these cases (5). Secondary uterine involvement can result from direct extension of malignancies from adjacent pelvic organs such as the rectum, urinary bladder, or peritoneum, or it may arise from widespread peritoneal dissemination (6). Hematogenous or lymphatic metastasis to the uterus from nongynecological primary tumors is exceedingly rare (6). Among extragenital malignancies, breast carcinoma is the most common primary tumor to metastasize to the gynecological tract, accounting for approximately half of all cases (7).

Within the uterus, metastatic tumors most often involve the myometrium. Endometrial metastases almost always coexist with myometrial involvement (6). However, a few rare cases have been reported in which metastatic extragenital tumors were confined exclusively to the endometrium or to an endometrial polyp (8-11). Such isolated endometrial metastases are exceptionally rare and may be misinterpreted as primary endometrioid or poorly differentiated carcinomas, leading to diagnostic challenges (9, 12-14).

Invasive lobular carcinoma (ILC) is the most common histological type of breast carcinoma that metastasizes to the uterus (15-17). Although invasive ductal carcinoma (IDC) is the most prevalent type of breast carcinoma overall, ILC accounts for approximately 10% of all invasive breast carcinomas (3). ILC is associated with a high propensity for distant metastasis (18). In addition to more typical metastatic sites such as the bone, lungs, pleura, soft tissue, and liver, ILC can metastasize to less common locations, including the gastrointestinal tract, peritoneum, ovaries, and uterus (6).

Tamoxifen is the most widely used adjuvant therapy for hormone receptor-positive breast carcinoma. Long-term tamoxifen use—up to 10 years—has been shown to reduce breast carcinoma mortality by half over a 20-year period after diagnosis (19, 20). However, due to its partial agonistic effect on the endometrial tissue, prolonged tamoxifen

therapy is associated with an increased risk of endometrial pathologies, including polyps, non-atypical hyperplasia, atypical hyperplasia, and endometrial carcinoma (19, 21, 22). Although tamoxifen does not appear to increase the risk of endometrial carcinoma in premenopausal women, postmenopausal women require close monitoring for signs of endometrial pathology (23, 24). Routine endometrial surveillance is not currently recommended unless patients are at high risk for endometrial carcinoma. However, if atypical hyperplasia develops, appropriate gynecologic management is warranted, and the continuation of tamoxifen should be reconsidered.

Herein, we report a case of metastatic ILC of the breast involving a tamoxifen-associated endometrial polyp in a patient with a history of bilateral breast carcinoma. Despite surgical resection followed by adjuvant chemotherapy and hormonal therapy, breast carcinoma—particularly ILC—has a high metastatic potential. Although uterine metastases from breast carcinoma are rare, any abnormal endometrial pathology in patients with a history of breast carcinoma should prompt consideration of metastatic disease. Accurate distinction between primary and metastatic endometrial lesions is essential, as treatment strategies differ. We emphasize the importance of a thorough diagnostic workup and a heightened clinical suspicion for metastatic disease in patients with a history of breast carcinoma, particularly those with ILC.

Case Report

This study was approved by the Institutional Review Board of Samsung Medical Center (2024-09-073). Due to the retrospective design of the study, the requirement for written informed consent was waived. A 42-year-old premenopausal Korean woman with a history of bilateral breast carcinoma presented to our gynecologic oncology outpatient clinic. Eight years earlier, at the age of 34, she had undergone partial mastectomy (breast-conserving surgery) for invasive carcinoma of the right breast. Histologically, the tumor was classified as IDC (Figure 1A), measuring 1.2 cm at its greatest dimension. The surgical resection margins

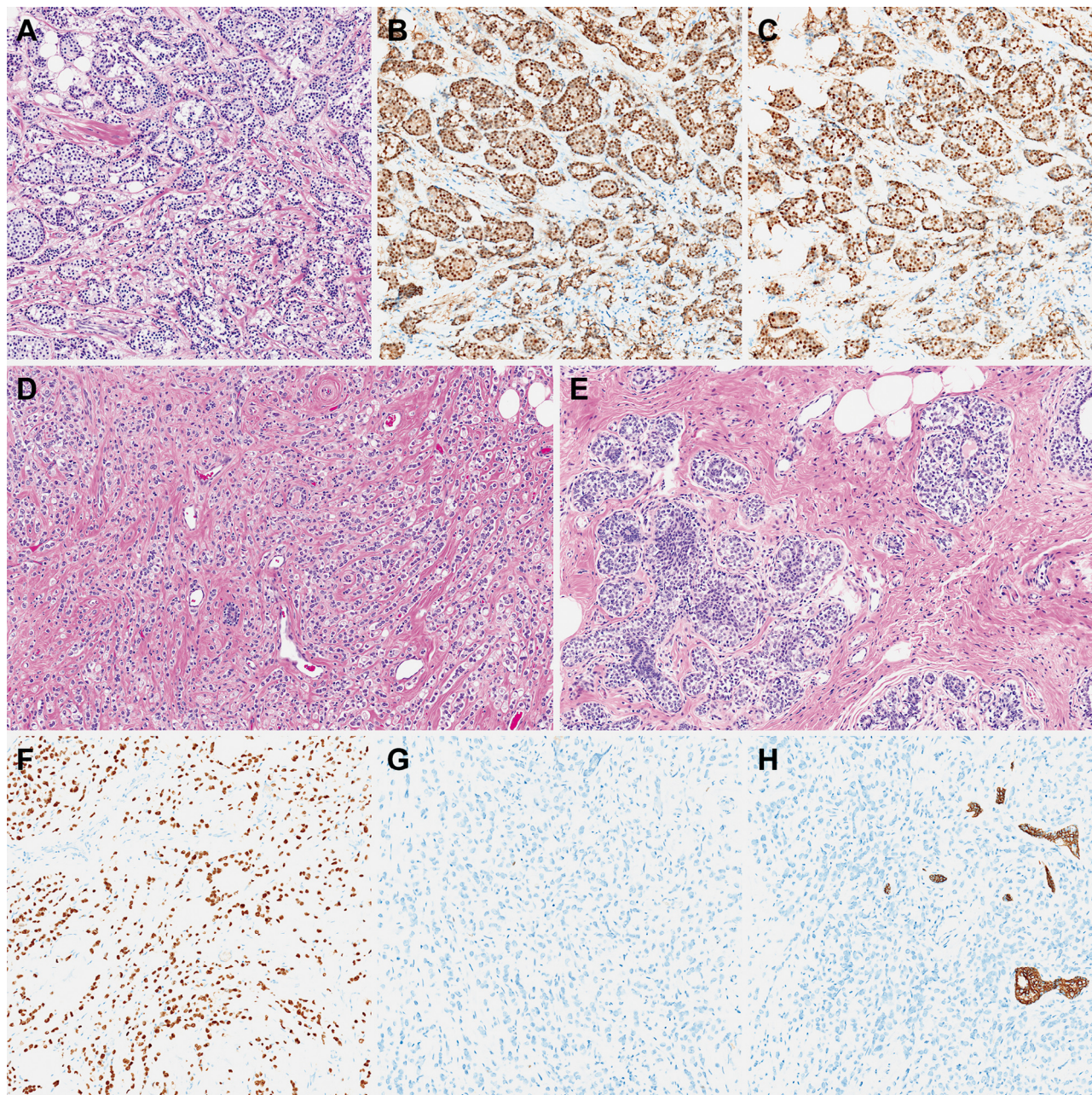


Figure 1. Microscopic findings of primary breast carcinomas. (A-C) Invasive ductal carcinoma (IDC) of the right breast. (A) Typical histological features of IDC. Diffuse and strong positivity for (B) estrogen receptor and (C) progesterone receptor in IDC. (D-H) Invasive lobular carcinoma (ILC) of the left breast. Typical histological features of (D) ILC and (E) lobular carcinoma in situ. (F) Diffuse and strong positivity for estrogen receptor. (G) Negative expression for progesterone receptor. (H) Loss of E-cadherin expression in ILC. Original magnification: A-C, 40 \times ; D-H, 100 \times .

were free of invasive carcinoma and ductal carcinoma *in situ*. Lymphovascular invasion was present; however, both the sentinel and non-sentinel axillary lymph nodes were

negative for metastasis. Immunohistochemical analysis revealed tumor cell positivity for the estrogen receptor (ER; Figure 1B) and progesterone receptor (PR; Figure 1C). The

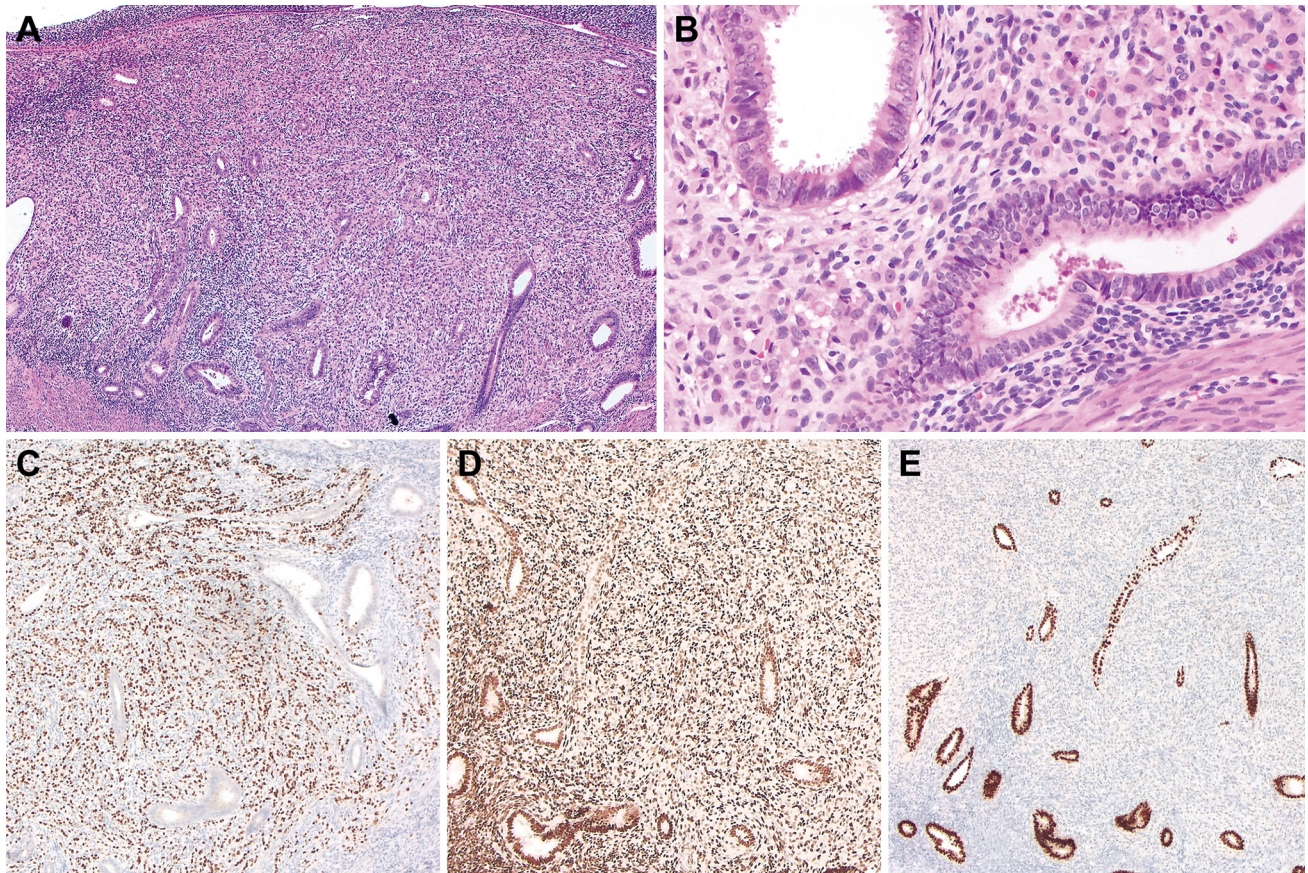


Figure 2. Microscopic findings of metastatic invasive lobular carcinoma (ILC) involving a tamoxifen-related endometrial polyp. (A) Clusters of tumor cells occupying the stroma between endometrial glands. (B) Metastatic ILC cells showing enlarged nuclei and eosinophilic cytoplasm, with adjacent non-neoplastic endometrial glands lined by pseudostratified columnar epithelium. (C) Diffuse and strong positivity for GATA-binding protein 3 in metastatic ILC. (D) Diffuse and strong positivity for estrogen receptor in both metastatic ILC cells and endometrial glands. (E) Lack of paired box 8 expression in metastatic ILC. Original magnification: A, 40 \times ; B, 200 \times ; C-E, 40 \times .

patient subsequently received four cycles of adjuvant chemotherapy with doxorubicin and cyclophosphamide, followed by adjuvant radiotherapy.

Five years postoperatively, at the age of 39, she developed a large mass in the left breast. A left total mastectomy was performed. Histologically, the tumor was diagnosed as ILC (Figure 1D). The total tumor, including the lobular carcinoma *in situ* (LCIS) component (Figure 1E), measured 12 cm in its greatest dimension, with an invasive component measuring 11.5 cm. The surgical margins were clear of both invasive carcinoma and LCIS. Lymphovascular invasion was not observed, and the sentinel and non-sentinel axillary lymph nodes were

negative for metastasis. Immunohistochemically, the tumor cells were positive for ER (Figure 1F), negative for PR (Figure 1G), and showed loss of E-cadherin expression (Figure 1H), consistent with a diagnosis of ILC.

In addition to breast carcinoma, the patient had undergone a left radical nephrectomy at 33 years of age for a grade 2 neuroendocrine tumor (NET) of the kidney. Four years later, she underwent partial hepatectomy and received adjuvant chemotherapy for hepatic metastasis of the NET. One year after nephrectomy, she underwent left adrenalectomy followed by radioisotope therapy for adrenal metastasis of the NET. Despite the early onset of multiple malignancies, there was no family history of carcinoma.

Germline genetic testing for breast cancer 1 (*BRCA1*) and *BRCA2* mutations revealed no pathogenic variants.

Following a total mastectomy for ILC of the left breast, the patient received adjuvant therapy consisting of a gonadotropin-releasing hormone analog and tamoxifen. She has remained free of recurrent disease. However, 3 years postoperatively, routine transvaginal ultrasonography revealed an irregularly thickened endometrium measuring up to 2.3 cm. The patient was asymptomatic and reported no gynecological complaints. An endometrial polyp was suspected, and a hysteroscopic polypectomy was performed.

Histopathological evaluations, including hematoxylin and eosin staining and immunohistochemistry, were performed. Microscopically, the polypoid lesion consisted of variably sized, irregularly shaped glands lined by stratified cuboidal to columnar epithelium embedded within a dense fibrovascular stroma. Some glands exhibited cystic dilation or branching with irregular contours and contained eosinophilic intraluminal secretions. The glandular epithelium exhibited mildly hyperchromatic, yet otherwise unremarkable, small nuclei and moderate amounts of cytoplasm. Tubal and mucinous metaplastic foci were also observed. Staghorn-shaped glands and mild periglandular stromal condensation were present; however, the degree of stromal condensation and cytological atypia was insufficient for a diagnosis of adenocarcinoma. The stroma also featured prominent, thick-walled, dilated blood vessels. These histological features – namely, a densely fibrotic stroma, cystically dilated glands with metaplastic epithelial changes, and mild periglandular condensation – were consistent with a diagnosis of tamoxifen-associated endometrial polyp.

Additionally, discrete foci of atypical cells were identified within the polyp stroma (Figure 2A). These cells were arranged in irregular, linear strands (one to two cells thick), as well as small tubules or nests, and were dispersed throughout the dense fibrotic stroma. They appeared non-cohesive and monotonous, with enlarged, hyperchromatic, pleomorphic nuclei and moderate amounts of eosinophilic cytoplasm (Figure 2B). Some cells exhibited intracytoplasmic lumina and

eccentrically located nuclei, producing plasmacytoid or signet-ring-like morphologies. Mitoses were frequently observed. The adjacent non-neoplastic endometrium was weakly proliferative, containing small tubular glands lined by pseudostratified columnar epithelium and cellular stroma. Immunohistochemically, the atypical stromal cells were positive for GATA-binding protein 3 (Figure 2C) and ER (Figure 2D), but negative for paired box 8 (Figure 2E), supporting a diagnosis of metastatic carcinoma of breast origin. Based on the morphology and immunoprofile, the final pathological diagnosis was metastatic ILC of the left breast involving a tamoxifen-associated endometrial polyp.

Given the known tendency for breast carcinoma metastases to the endometrium to occur alongside widespread disease, a systematic workup was conducted. However, no evidence of recurrence or metastasis was observed in any other organ or anatomical site. Even within the uterus, imaging revealed no abnormalities apart from uterine leiomyomas. The patient subsequently underwent a total hysterectomy with bilateral salpingo-oophorectomy. A thorough histopathological examination of the surgical specimen revealed no residual carcinoma. To date, the patient remains alive and disease-free.

Discussion

To our knowledge, this is the first report of metastatic ILC confined to a tamoxifen-associated endometrial polyp in a patient with metachronous bilateral breast carcinoma. The patient had previously been diagnosed with IDC of the right breast eight years prior and ILC of the left breast three years before endometrial metastasis was detected. The two primary tumors were similar in size, and both showed uniform ER positivity. Surgical management included unilateral partial mastectomy with sentinel lymph node dissection for each lesion, followed by postoperative chemotherapy and hormonal therapy. Although lymphovascular invasion was present only in the earlier IDC, it was the subsequent ILC that metastasized to the endometrial polyp.

IDC and ILC are the two most common histological types of breast carcinoma. IDC accounts for approximately 76% of cases, while ILC accounts for approximately 8% (25). Despite its lower incidence, ILC is disproportionately more likely to metastasize to the female genital tract (7). In a large autopsy-based study, Lamovec and Bracko (26) demonstrated that ILC exhibits a greater predilection for metastasis to the peritoneum, hollow viscera, and gynecologic organs than IDC. These metastatic lesions are characterized by diffusely infiltrating tumor cells in a pattern reminiscent of lymphoid malignancies. In contrast, IDC more commonly metastasizes to the liver and bones, suggesting that histological subtypes may have distinct organotropism.

Further studies by Chen *et al.* (27) and Harris *et al.* (28) corroborated that ILC exhibits a distinctive metastatic profile, with a higher likelihood of spreading to the meninges, peritoneum, gastrointestinal tract, and uterus than IDC. This behavior has been attributed to the loss of E-cadherin expression in ILC, resulting in a discohesive phenotype and impaired cell-cell adhesion—features not typically observed in IDC (29, 30). Inactivation of the *CDH1* gene, which encodes E-cadherin, is an early event in ILC oncogenesis, occurring *via* somatic truncating mutations, loss of heterozygosity, or promoter methylation (31). The loss of E-cadherin is thought to facilitate tumor cell dissemination and distant seeding (32, 33).

Interestingly, previous studies have observed that adenocarcinomas with signet ring-like morphology metastasize to gynecological organs more frequently than those with tubular or ductal morphology (34). Notably, both signet ring cell carcinoma of the stomach and ILC of the breast share histological features of poorly cohesive cells with abundant intracytoplasmic mucin and are among the most common extragenital tumors that metastasize to the female genital tract (34). Moreover, both tumor types typically exhibit E-cadherin loss, contributing to their ability to undergo epithelial-mesenchymal transition (35, 36).

Breast carcinoma metastases confined solely to the endometrium are exceedingly rare, and the underlying mechanisms remain incompletely understood (1). Several plausible routes of spread have been proposed. First,

hematogenous dissemination is considered the most likely pathway, particularly for ILC, which demonstrates a pronounced tendency for blood-borne metastasis. The richly vascularized endometrium may provide a permissive environment for metastatic implantation (37). Second, lymphatic spread through the pelvic or abdominal routes may result in uterine metastasis; however, this typically manifests as myometrial involvement rather than isolated endometrial lesions (38). Third, tamoxifen, a selective estrogen receptor modulator widely used as adjuvant endocrine therapy for ER-positive breast carcinoma, acts as an estrogen agonist in the endometrium, promoting the development of polyps and hyperplasia. This hormonally altered microenvironment may facilitate the implantation and survival of metastatic tumor cells (39).

The American College of Obstetricians and Gynecologists (40) does not recommend routine endometrial carcinoma screening for asymptomatic women receiving tamoxifen. Although some emerging evidence supports pretreatment transvaginal ultrasonography in postmenopausal patients, no additional surveillance is currently recommended for premenopausal women, as tamoxifen does not increase their risk of endometrial carcinoma. Nevertheless, the utility of endometrial evaluation extends beyond screening for primary endometrial neoplasia. Given that isolated, asymptomatic endometrial metastases may occur in premenopausal patients with ILC, clinicians should maintain a high index of suspicion for metastatic disease, even in the absence of gynecologic symptoms.

Conclusion

We report a rare case of ILC of the breast metastasizing exclusively to an endometrial polyp in a patient receiving tamoxifen therapy. This case highlights the distinctive metastatic behavior of ILC, which may present with subtle and unexpected patterns of dissemination. Clinicians should maintain a high index of suspicion and consider the possibility of metastatic disease even in asymptomatic patients, particularly those with a history of ILC, to ensure timely diagnosis and appropriate management.

Conflicts of Interest

The Authors declare no conflicts of interest or financial ties in relation to this report.

Authors' Contributions

All Authors made substantial contributions to the conception and design of this work; the acquisition and interpretation of data; drafting and critical revision of the manuscript for important intellectual content; and approval of the final version to be published.

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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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