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Management of HER2-Positive Invasive Micropapillary Breast Cancer: Focus on Chemotherapy Toxicities and Surgical Implications of Typhlitis

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Rezumat

Managementul neoplasmului mamar micropapilar invaziv HER-2 pozitiv: accent pe toxicitățile chimioterapiei și implicațiile chirurgicale ale tiflitei

Introducere: Cancerul de sân rămâne cea mai frecventă malignitate, în rândul femeilor la nivel mondial şi o cauză majoră de mortalitate prin cancer. Carcinomul micropapilar invaziv (IMPC), deşi cu o frecvență relativ rară, prezintă un comportament biologic agresiv, caracterizat prin invazie limfovasculară şi o tendință marcată de metastazare ganglionară. Subtipul IMPC HER2-pozitiv ridică provocări terapeutice deosebite, necesitând terapie biologică țintită, dar fiind asociat şi cu un risc crescut de evenimente adverse legate de tratament. *Obiectiv:* Aceast articol îşi propune să sintetizeze dovezile actuale privind caracteristicile clinicopatologice şi tratamentul IMPC HER2-pozitiv, cu un accent special pe complicația emergentă reprezentată de tiflită în contextul chimioterapiei pe bază de taxani.
Metode: A fost realizată o revizuire narativă a literaturii pentru a rezuma datele referitoare la mecanismele patogenice, prezentarea clinică, aspectele diagnostice şi strategiile de management asociate IMPC HER2-pozitiv şi tiflitei induse de chimioterapie.
Rezultate: Dovezile existente subliniază evoluția agresivă a IMPC, relevanța terapeutică a regimurilor direcționate anti-HER2 şi apariția rară, dar potențial letală, a enterocolitei neutropenice la pacienții tratați cu taxani. Deşi datele sunt limitate, cazurile raportate evidențiază importanța recunoaşterii precoce şi a managementului multidisciplinar.
Concluzii: IMPC HER2-pozitiv reprezintă un subtip rar, dar clinic semnificativ de cancer mamar, cu implicații terapeutice şi prognostice distincte. Regimurile pe bază de taxani rămân o piatră de temelie a tratamentului, însă necesită o vigilență crescută pentru tiflită, care, deşi neobişnuită, este asociată cu o morbiditate şi mortalitate semnificative. Sunt necesare studii suplimentare pentru a defini strategiile optime de stratificare a riscului, prevenție şi tratament.

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Cuvinte cheie: cancer mamar, IMPC, HER2, chimioterapie pe bază de taxani, pertuzumab, trastuzumab, tiflită

Abstract

Background: Breast cancer remains the most prevalent malignancy in women worldwide and a leading cause of cancer-related mortality. Invasive micropapillary carcinoma (IMPC), though relatively uncommon, exhibits aggressive biological behavior, characterized by lymphovascular invasion and a marked propensity for nodal metastasis. The HER2-positive subtype of IMPC poses particular therapeutic challenges, necessitating targeted biological therapy but also conferring an increased risk of treatment-related adverse events. *Objective:* This review aims to synthesize current evidence on the clinicopathological features and treatment of HER2-positive IMPC, with a special emphasis on the emerging complication of typhlitis in the context of taxane-based chemotherapy.

Methods: A narrative review of the literature was conducted to summarize data regarding pathogenic mechanisms, clinical presentation, diagnostic considerations, and management strategies related to HER2-positive IMPC and chemotherapy-associated typhlitis.

Results: Existing evidence highlights the aggressive course of IMPC, the therapeutic relevance of HER2-directed regimens, and the rare but potentially life-threatening occurrence of neutropenic enterocolitis in patients receiving taxanes. Although data remain limited, reported cases underscore the importance of early recognition and multidisciplinary management.

Conclusions: HER2-positive invasive micropapillary carcinoma is a rare but aggressive breast cancer subtype requiring multimodal therapy. While dual HER2 blockade with taxane-based chemotherapy improves survival, it also increases the risk of severe complications such as typhlitis. Early recognition and timely surgical intervention are essential to reduce morbidity and mortality. With appropriate therapeutic adjustments, systemic treatment can be safely continued, emphasizing the need for better risk stratification and preventive strategies.

Keywords: breast cancer, IMPC, HER2, taxane-based chemotherapy, pertuzumab, trastuzumab, typhlitis

Introduction

Breast cancer remains the most commonly diagnosed malignancy among women and continues to represent the leading cause of cancer-related mortality on a global scale. Prognosis and therapeutic responsiveness are significantly determined by the underlying molecular subtype. Invasive micropapillary carcinoma (IMPC), although relatively rare (accounting for 2-8% of breast cancers), is characterized by its high aggressiveness, lymphovascular invasion, and strong tendency for regional lymph node metastasis. The HER2-positive variant of IMPC poses particular therapeutic challenges, requiring the use of targeted biological agents while simultaneously being associated with an increased risk of severe treatment-related adverse events.

Among these, typhlitis (neutropenic enterocolitis) represents a rare but potentially life-threatening complication, increasingly described in patients undergoing taxane-based chemotherapy. The purpose of this review is to provide a comprehensive synthesis of current evidence regarding IMPC, with a focus on established therapeutic approaches and the emerging concern of typhlitis. Specifically, we will address pathogenic mechanisms, clinical manifestations, diagnostic hallmarks, and contemporary management strategies.

Methodology

This review is based on articles retrieved from the medical literature reporting cases of HER2-positive breast cancer complicated by typhlitis (neutropenic enterocolitis). A systematic search was performed in the PubMed/MEDLINE, Scopus, and Web of Science databases for articles published between January 1986 and June 2025.

Inclusion and Exclusion Criteria

Inclusion criteria comprised studies describing the therapeutic management of patients with the invasive micropapillary carcinoma (IMPC) subtype of HER2-positive breast cancer who developed typhlitis during chemotherapy cycles. In addition, articles addressing the pathogenic mechanisms and therapeutic management of typhlitis in the context of solid tumors were included to provide broader clinical insight.

Articles were excluded if they were conference abstracts, animal studies, non-English publications, or if the full text was unavailable. Relevant

references from selected articles were also screened to identify additional eligible studies.

Epidemiology and Characteristics of HER2+ Breast Cancer - IMPC Subtype

Breast cancer is the most commonly diagnosed malignant tumor and the leading cause of cancer-related mortality among women globally. Its complexity is underscored by significant biological heterogeneity. Molecular classification based on the RPM50 gene expression profile categorizes breast cancer into five intrinsic subtypes: luminal A, luminal B, basal-like, normal-like, and HER2-enriched. HER2-positive breast cancer, which accounts for approximately 13-15% of all cases, is associated with an especially poor prognosis (1)

In the context of our study, invasive micropapillary carcinoma (IMPC) is a rare subtype of breast cancer (2%-8%) characterized by unique histological and biological features. Morphologically, it consists of morula-like, nested, or pseudopapillary clusters of neoplastic cells lacking fibrovascular cores, typically surrounded by clear stromal spaces that mimic lymphovascular channels (2). In 1980, Fisher et al. (3) first described the "exfoliative appearance structure" observed in breast tissue. Subsequently, in 1993, Siriaunkgul and Tavassoli (4) introduced the term "invasive micropapillary carcinoma of the breast" and provided a detailed histopathological characterization of this entity. It was not until 2003 that the World Health Organization (WHO) officially recognized IMPC as a distinct histological subtype of breast cancer - a classification that remains valid today (5). Invasive micropapillary carcinoma (IMPC) is characterized by angioinvasive behavior, promoting vascular spread and a higher likelihood of lymph node metastasis, which correlates with poorer clinical outcomes. This subtype also commonly expresses HER2 and estrogen receptors (ER) (6). Despite its rarity, IMPC is notably associated with an increased risk of lymph node metastasis (LNM), lymphovascular invasion (LVI), and locoregional recurrence (LRR). Advances in the study of this subtype have significantly enhanced the understanding of its epidemiological profile, clinicopathological features, and diagnostic criteria (7).

Treatment Protocols for HER2+ Breast Cancer

International consensus guidelines (8) currently recommend dual HER2 blockade with trastuzumab and pertuzumab, in combination with systemic chemotherapy, as the standard of care for patients with HER2-positive breast cancer. Within this framework, taxane-based regimens - most commonly incorporating paclitaxel or docetaxel - are widely employed as the backbone of systemic therapy.

The selection of the appropriate taxane in the treatment of HER2-positive breast cancer requires balancing antitumor efficacy against the toxicity profile and the therapeutic context, particularly in the era of targeted anti-HER2 therapy. A comprehensive review of clinical experience indicated that docetaxel was frequently preferred by clinicians due to its favorable pharmacokinetic profile, shorter infusion time, and consistent clinical activity across several disease settings. Evidence from a pivotal randomized phase III trial (9) in metastatic breast cancer previously treated with anthracyclines demonstrated the superiority of docetaxel over paclitaxel when administered every three weeks at standard doses. In this study, docetaxel achieved a significantly longer OS (median 15.4 vs. 12.7 months; HR 1.41, $p = 0.03$) and TTP (median 5.7 vs. 3.6 months; HR 1.64, $p < 0.0001$) compared with paclitaxel, although with increased rates of hematologic and non-hematologic toxicities. Quality of life measures were overall comparable between arms.

Regarding the dual HER2 blockade with trastuzumab and pertuzumab, it is well known that it is the standard of care. Trastuzumab is a humanized monoclonal antibody, approved by the EMA in 2000, that binds selectively to the HER2 receptor, inhibiting the proliferation of cells that overexpress HER2. It is also a mediator of antibody-dependent cellular cytotoxicity (ADCC). On the other hand, pertuzumab, also a humanized monoclonal antibody, approved by EMA in 2013, binds to subdomain II of the HER2 receptor and blocks heterodimerization and signal transduction via MAPK (mitogen-activated protein kinase) and PI3K (phosphoinositide 3-kinase)/protein kinase-B (AKT) pathways essential for tumor growth (10).

The beneficial impact of HER2+ blockade is most convincingly demonstrated in the CLEOPATRA trial (11), which established the superior efficacy of dual HER2+ inhibition in combination with docetaxel. Median overall survival was extended to 56.5 months compared to 40.8 months, while median progression-free survival was likewise prolonged by 6.3 months. The tolerability profile was deemed acceptable, including with regard to left ventricular dysfunction. The safety profile of the dual blockade regimen was consistent

with expectations: the most frequent adverse events included diarrhea, rash, and febrile neutropenia, with higher rates of grade ≥3 diarrhea and neutropenia observed in the pertuzumab arm, while cardiac dysfunction did not differ significantly between groups. These findings underscored both the efficacy and manageable tolerability of dual HER2 blockade, validating the strategy of simultaneously targeting distinct HER2 epitopes.

Taken together, current evidence consolidates dual HER2 blockade with trastuzumab and pertuzumab, in combination with taxane-based chemotherapy, as the therapeutic cornerstone in HER2-positive breast cancer. The CLEOPATRA trial not only established a significant and durable survival advantage, but it also highlighted the feasibility of long-term treatment with an acceptable safety profile. Nonetheless, the choice of taxane backbone and the management of treatment-related toxicities remain critical considerations, underscoring the need for individualized therapeutic strategies and continued refinement of anti-HER2 treatment.

Pathogenesis of Typhlitis and its Clinical Impact

Typhlitis, also known as neutropenic enterocolitis (NE), is a necrotizing inflammation that predominantly affects the cecum and surrounding intestinal tissues. It is recognized as the most frequent gastrointestinal complication among patients with leukemia. Over time, however, cases in adults with malignancies have increased, particularly hematological disorders such as leukemia, lymphoma, multiple myeloma, aplastic anemia, and myelodysplastic syndromes, as well as other immunosuppressive conditions including AIDS, solid tumor therapies, and organ transplantation (12). The reported incidence of neutropenic enterocolitis (NE) varies across studies. In a systematic review by Gorschlüter et al. (13), which included 21 studies, the incidence was 5.3% among patients hospitalized for hematologic malignancies, high-dose chemotherapy for solid tumors, or aplastic anemia. In contrast, a separate cohort study identified NE in 3.5% of 317 severely neutropenic patients (14). Given that various segments of the gastrointestinal tract can be involved, the broader term neutropenic enterocolitis is now considered more appropriate.

Although its clinical significance is well established, the exact pathogenesis of typhlitis remains unclear (15). One proposed mechanism involves the development of mucositis, which disrupts the integrity of the mucosal barrier and facilitates bacterial translocation from the intestine. Histological studies support this mechanism, revealing intestinal wall edema, vascular congestion, and mucosal surface rupture, often accompanied by ulceration and bleeding. Neutropenia further increases susceptibility by impairing immune defenses and reducing the ability to control transmural pathogen translocation. In addition, some authors suggest that direct invasion of the intestinal wall by malignant cells may play a role. The cecum is most frequently affected due to its distensibility and relatively poor blood supply, features that can exacerbate the clinical course. Although this mechanism provides a plausible explanation for many cases, it is likely that NE arises from a combination of immunologic, infectious, and treatment-related factors (16).

The clinical presentation is nonspecific and typically includes abdominal pain, fever, and diarrhea, with imaging studies frequently demonstrating bowel wall thickening. Given the absence of a specific clinical presentation for typhlitis, establishing a differential diagnosis is crucial in routine clinical practice. Neutropenic enterocolitis can resemble a variety of other conditions. Differential diagnoses include pseudomembranous colitis, inflammatory bowel disease, appendicitis, ischemic colitis, and other infectious forms of colitis (17). Management strategies vary from conservative medical therapy to surgical intervention in complicated cases (18).

Illustrative Clinical Case

A 44-year-old patient diagnosed with invasive micropapillary breast carcinoma M1 LYM (right axilla ER-; PR-; HER2 3+; KI-67 30%, BRCA 1, 2 - . was planned for neoadjuvant chemotherapy with Docetaxel, Carboplatin, and Pertuzumab + Trastuzumab. One week after the first chemotherapy session, she was admitted to the hospital for severe pain localized into the hypogastrium associated with fever and diarrhea. The patient underwent a CT scan of the thorax, abdomen, and pelvis, which revealed a segmental circumferential wall thickening of the cecum, ileocecal valve, terminal ileum, and proximal ascending colon, with mucosal stratification, submucosal edema, adjacent fat stranding, and small locoregional lymphadenopathy - suggestive of typhlitis (*Figs. 1, 2)*.

She initiated antibiotic and antifungal therapy. Due to the persistent inflammatory state, the

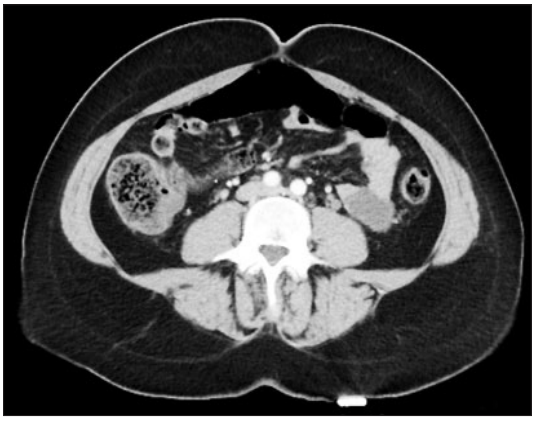

Figure 1. Contrast-enhanced computed tomography of the abdomen, showing parietal wall thickening (initial investigation).

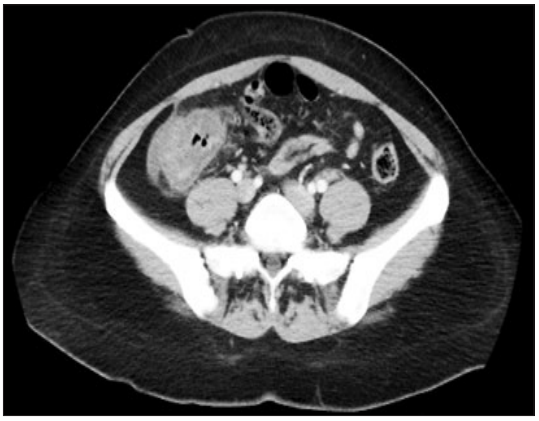

Figure 2. Contrast-enhanced computed tomography of the abdomen obtained at a more caudal level, demonstrating bowel wall thickening.

patient underwent a second CT, which revealed parietal changes with an inflammatory-infectious substrate involving the cecum, ascending colon, and terminal ileal loop. A slight progression of the inflammatory involvement was noted in the ascending colon, accompanied by worsening of adjacent inflammatory changes, pericecal fluid accumulation, and thickening of the surrounding peritoneum. Due to persistent abdominal pain and a slow decline in inflammatory marker levels, a surgical evaluation was warranted. The patient was subsequently transferred to the surgery department. Surgical intervention was performed with the diagnosis of typhlitis complicated by acute peritonitis secondary to cecal perforation. A right hemicolectomy with manual latero-lateral ileo-transverse anastomosis was undertaken.

After the patient was discharged from the hospital and recovered postoperatively, the oncological treatment was resumed with a slight modification of the therapeutic regimen (Paclitaxel instead of Docetaxel) and the reintroduction of the loading dose for Pertuzumab / Trastuzumab shot, followed at 24h post-chemotherapy by Pegfilgrastinum sc. She had, in total, 7 series of chemotherapy. During the last chemotherapy session, the patient developed an adverse reaction 17 minutes following the initiation of carboplatin infusion. Clinical manifestations included abrupt onset of paresthesias localized to the facial region and upper extremities, recurrent episodes of vomiting, nausea, and dizziness. Symptomatology resolved following administration of supportive care. Consequently, the clinical decision was made to discontinue the carboplatin infusion and to withhold further administration.

Upon completion of systemic therapy, the patient underwent the breast MRI and total CT which demonstrated a favorable therapeutic response. Additionally, the multidisciplinary tumor board recommended surgical intervention consisting of a right radical mastectomy, followed by the continuation of systemic therapy with Pertuzumab/Trastuzumab in conjunction with radiotherapy. At present, the patient maintains oncological stability, supported by biological and imaging findings (*Figs. 3, 4)*.

Discussion

Invasive micropapillary carcinoma (IMPC) represents a rare histopathological subtype of breast cancer, with a low incidence and the absence of dedicated therapeutic guidelines. Consequently, management strategies are largely extrapolated from those established for invasive ductal carcinoma. Advances in multimodal therapy, including surgery, chemotherapy, endocrine therapy, targeted agents, and immunotherapy, have considerably improved disease control and quality of life; however, IMPC continues to present unique clinical challenges. Notably, this subtype is characterized by a striking propensity for lympho-vascular invasion, with reported rates of nodal involvement reaching up to 84%, reflecting its strong lymphotropic biology. Furthermore, IMPC can be classified into pure and mixed forms, with pure IMPC demonstrating more aggressive clinical behavior, a lower rate of locoregional recurrence-

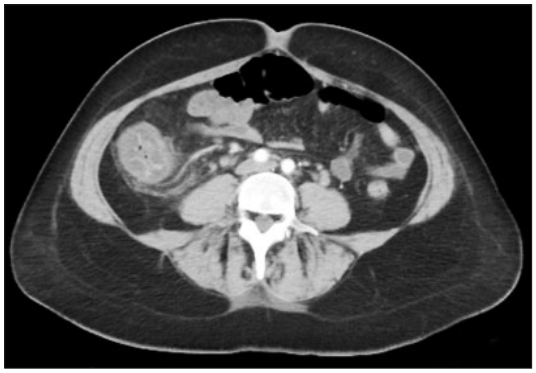

Figure 3. The second abdominal CT- prior to surgery. Parietal changes with an inflammatory-infectious substrate involving the cecum, ascending colon, and terminal ileal loop.

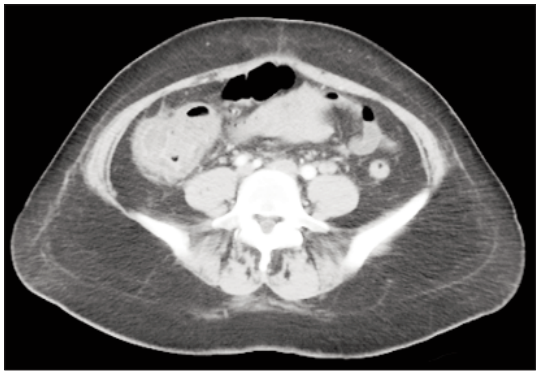

Figure 4. The second abdominal CT- prior to surgery. Parietal changes with an inflammatory-infectious substrate.

free survival, and a higher frequency of locoregional recurrence compared to mixed IMPC (19).

While targeted therapies combined with chemotherapy significantly improve prognosis, treatment-related complications such as typhlitis remain a concern. Neutropenic enterocolitis is a severe inflammatory condition that predominantly affects the cecum and is more often associated with cytotoxic chemotherapy, particularly regimens based on taxanes. These agents have been associated with a wide spectrum of colitis. While comparing the toxic effects of docetaxel and paclitaxel is challenging, docetaxel appears to induce more adverse effects. The most frequent presentation is ischemic colitis, clinically characterized by acute abdominal pain accompanied by neutropenia, fever, and/or diarrhea, sometimes with blood. This condition can progress to severe complications, including intestinal necrosis, colonic perforation, or typhlitis. Septicemia is common, typically due to aerobic Gram-negative bacterial infections. Histopathological examination of the mucosa reveals pronounced inflammatory changes, including mucosal and submucosal edema, hemorrhage, acute inflammatory infiltrates, and mucosal ulceration. The condition typically presents with nonspecific symptoms such as fever, abdominal pain, and diarrhea. Computed tomography (CT) is the diagnostic modality of choice, frequently demonstrating features such as bowel wall thickening and pneumatosis intestinalis (20).

The pathogenesis of typhlitis remains poorly understood. However, the systemic toxicity of chemotherapeutic agents on rapidly proliferating tissues, including the gastrointestinal mucosa, appears to play a central role. The increased vulnerability of the cecum may be related to its anatomical and physiological characteristics, including greater distensibility, reduced vascular perfusion, and enhanced lymphatic drainage. While initial management is often conservative, the clinical course can rapidly progress. Complications such as bowel perforation and peritonitis may occur, necessitating prompt surgical intervention. In the present case, early conservative measures were insufficient, and surgical treatment was ultimately required.

This case highlights an atypical presentation of typhlitis, characterized by the absence of neutropenia at the onset of clinical symptoms. Despite the presence of classical feature, such as fever, abdominal pain, and diarrhea, the biological profile did not initially support the diagnosis, making early recognition challenging. A notable aspect is the prior administration of pegfilgrastim, which raises the question of whether this granulocyte colony-stimulating factor may have masked an underlying neutropenic state. Indeed, while pegfilgrastim effectively accelerates neutrophil recovery and can normalize peripheral neutrophil counts, this hematologic correction does not resolve the underlying mucosal injury or intestinal inflammation associated with neutropenic enterocolitis. Consequently, laboratory values alone may underestimate the patient's residual risk, and clinicians should maintain a high index of suspicion, relying on clinical assessment and imaging studies for timely diagnosis and management. Further investigation is warranted to better understand the impact of growth factor support on the diagnostic and clinical course of typhlitis in patients undergoing cytotoxic chemotherapy.

Conclusion

HER2-positive invasive micropapillary carcinoma (IMPC) remains a rare but clinically aggressive breast cancer subtype with distinct pathological features and therapeutic challenges. Dual HER2 blockade combined with taxane-based chemotherapy provides significant survival benefits, but also increases the risk of severe adverse events, including neutropenic enterocolitis (typhlitis).

Although uncommon, typhlitis represents a potentially life-threatening complication that requires early recognition, prompt multidisciplinary management, and, in complicated cases, surgical intervention such as right hemicolectomy. Importantly, even after major gastrointestinal complications, continuation of systemic therapy is feasible through careful adjustment of the chemotherapeutic regimen and supportive measures, without compromising oncological outcomes.

From a surgical standpoint, timely decision-making is crucial in preventing morbidity and mortality associated with bowel perforation and peritonitis. Future research should aim to establish clearer risk stratification models, preventive strategies, and evidence-based guidelines for the management of typhlitis in patients with HER2-positive breast cancer treated with modern regimens, including Phesgo.

Conflicts of Interest

The authors declared no potential conflicts of interest.

Ethical Statement

This study was conducted in accordance with applicable ethical standards. All procedures involving the patient complied with the General Data Protection Regulation (GDPR).

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