Gastric Metastasis of Invasive Lobular Breast Carcinoma, a Current Diagnostic and Treatment Challenge - A Review

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Rezumat

Metastaza gastrică a carcinomului de sân lobular invaziv, o provocare actuală de diagnostic și tratament - o revizuire a literaturii

Introducere: Predilecția metastazei cancerului invaziv lobular de sân pentru stomac este un subiect care a ridicat diverse discuții de-a lungul timpului.

Istoric și Obiective: Metastaza gastrică a cancerului lobular de sân este neobișnuită și poate fi diagnosticată după o perioadă lungă de timp de la diagnosticul de tumoră primară. Scopul acestui studiu a fost de a revizui cunoștințele actuale cu privire la metodele actuale de diagnostic și tratament al metastazelor gastrice ale cancerului de sân.

Metoda: O căutare sistematică a literaturii a fost efectuată în baza de date Pub-Med – Medline folosind termenii „metastaza gastrică a cancerului de sân lobular” și „caracteristici ale metastazelor gastrice” pentru a identifica articole relevante pentru metastaza gastrică a cancerului de sân lobular.

Rezultate: Mai multe lucrări au arătat că subiectul este rar prezentat fie sub formă de prezentări de caz sau miniserii prin rezumarea cazurilor sporadice. Datorită rarității și specificității metastazelor ca tip de gazdă și aspectul de latență după cancerul lobular de sân, metastaza gastrică este considerată atipică și ocacional confundată cu o malignitate primară a stomacului. Cele mai recente articole prezintă criteriile de diagnostic imuno-histo chimice ale acestei entități clinice și o nouă abordare terapeutică.

Concluzii: La pacienții cu metastază gastrică a cancerului de sân lobular, obținerea de material patologic și interpretarea biopsiilor poate fi o adevărată provocare pentru obținerea unui diagnostic
patologic corect, imunohistochimia ne oferă un diagnostic de certitudine. Introducerea unui protocol de supraveghere endoscopică pentru pacienţii cu cancer lobular de sân ar putea fi o propunere pentru detectarea precoce a metastazelor gastrice care să permită o terapie adecvată.

**Cuvinte cheie:** metastaze gastrice, cancer de sân lobular, teste imunohistochimice, endoscopie superioară

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**Abstract**

*Introduction*: The predilection of lobular invasive breast cancer metastasis for the stomach is a topic that has succumbed to various assumptions over the time.

*Background and Aims*: Gastric metastasis of lobular breast cancer is unusual and it can be diagnosed after a long period of time from primary tumor diagnosis. The aim of this study was to review current knowledge regarding the current methods of diagnosis and treatment of gastric metastasis of breast cancer.

*Methods*: A systematic literature search was performed in the Pub-Med –Medline database using the terms “gastric metastasis of lobular breast cancer” and “gastric metastasis features” to identify articles relevant to gastric metastasis of lobular breast cancer.

*Results*: Several papers have shown that the topic is rarely presented in the form of case presentations or miniseries by summing up sporadic cases. Due to its rarity and metastasis specificity as host type and appearance after latency of lobular breast cancer makes its gastric metastasis considered atypical and occasionally confused with a primary stomach malignancy. The most recent articles present the immunohistochemical diagnostic criteria of this clinical entity and a new therapeutic approach.

*Conclusion*: At patients with gastric metastasis of lobular breast cancer, obtaining pathologic material and biopsies interpretation can be a real challenge for getting a correct pathologic diagnosis, immunohistochemistry gives us definite diagnosis. The introduction of an endoscopic surveillance protocol for patients with lobular breast cancer could be a proposal for the detection of early gastric metastases allowing for appropriate therapy.

*Key words*: gastric metastases, lobular breast cancer, immunohistochemistry test, upper endoscopy

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**Introduction**

Breast cancer has one of the highest incidence rates in the last years with a increasing trend and it is a leading cause of cancer-associated mortality worldwide in women (1).

Owing to the advances in management of breast cancer, overall survival rates have increased; but, these therapies have not produced significant changes in the prognosis of patients with breast metastases. Distant metastases rather than the primary tumour itself are the cause of death, almost 90% of breast cancer-related deaths are due to tumour dissemination (2).

The incidence of gastrointestinal metastases based on the results of autopsy series was estimated by some authors to be approximately 4 – 35% (3). Gastrointestinal metastases can sometimes be seen in patients with cancers of the breast, kidney, lung and malignant melanoma. Breast cancer is the second type of cancer which determines gastrointestinal metastasis, after lung cancer (4). Mclemore reported gastro-intestinal metastases in 0,3% of the 12001 patients diagnosed as breast cancer (5).
Epidemiology

Stomach is an uncommon site for tumour metastasis, with an incidence of 0.2–1.7%, with the most frequent primaries being in the lung, breast, or melanoma (6,7).

Through long-term follow-up and post-mortem studies, the incidence of gastric metastases of breast cancer was estimated at 2–18% (8,9).

The invasive lobular cancer that represents 5%–10% of primary breast cancers, frequently involves unusual metastatic sites such as the gastrointestinal tract, the gynaecological organs, the peritoneum and meninges (10–14) in contrast to the invasive ductal cancer that follows the more conventional metastatic pattern of breast cancers and metastasizes in liver, lungs and brain (15,16).

Breast cancer pathologic subtypes which had metastasis of gastrointestinal tract are often invasive lobular more than invasive ductal carcinomas (17). Invasive lobular carcinoma or luminal-type breast cancer (ER positive) tends to metastasize to the stomach at a higher frequency compared with other types of breast cancer (18,19,20).

Some authors showed in a mini serie that ninety-seven percent of gastric metastasis from breast cancers are derived from invasive lobular carcinoma (21).

Pathogenesis

The most cases described in literature on gastric metastasis of breast cancer simulate a primary gastric carcinoma. In these cases first described primary breast cancer and consequent metastases arise in part from disseminated tumoral cells originating from the primary tumour and from residual disease persisting after systemic therapy. Gastric metastasis may appear many years after the treatment for invasive lobular breast carcinoma (10).

An explication could be the phenomenon of metastatic dormancy, associated with the presence of disseminated tumour cells with low proliferative and metabolic activities (22).

These cells are not capable of producing a secondary tumour at the time of sowing, but remain viable and can acquire invasive skills through genetic changes and interactions with the micro medium. This dormancy state could be a major problem limiting the efficacy of chemotherapy, which acts on active and proliferative target cells but does not eradicate latent metastases (23). Some authors support the idea that chemokines as well as inflammatory events seem to be implicated in metastasis process and they hypothesized that H. pylori, inflammatory cells, and chemokines might create a favorable environment attracting tumor cells (24).

Diagnostic

Clinico-Imagistic Features

Because current guidelines do not support a routine search for gastric metastases in patients with treated breast cancer, their clinical suspicion is difficult because their occurrence may be after a long period of time when the patient may be considered cured of breast cancer (25).

Gastric metastasis of breast cancer is rarely seen and it is very difficult to diagnose, perhaps because this is not our first hypothesis. But, anyway it is hard to differentiate from a primary gastric cancer on clinical, imagistical and pathological characteristics (26).

The patients, who have gastric metastasis of breast cancer, usually suffer from nonspecific gastrointestinal symptoms like indigestion, dyspepsia, anorexia, pyrosis, nausea, epigastric pain, early satiety, vomiting, bleeding and weight loss, often indistinguishable from the symptoms of a primary gastric cancer (27).

Radiological findings on computed tomodiagnosis or barium studies are nonspecific, and may be hard to distinguish from primary gastric cancer (28).

The most common type of gastric metastasis of breast cancer is stiffness of the whole stomach such as in linitis plastica, while the type of discrete tumor or external compression is less common (4,15). Some patients
may present gastric perforation secondary to gastric metastasis from breast cancer (29).

Some authors reported in diagnosis of gastric metastasis the use of 18F-2-deoxy-2-fluoro-D-glucose (FDG) positron emission tomography combined with computed tomography imaging that revealed FDG uptake across the thickness of the antral wall (30).

Another authors suggest that when we have a high index of clinical suspicion in those with non-specific gastric symptoms and a past history of invasive lobular breast cancer, an early endoscopy are recommended (31).

Endoscopic aspects are no specific to suggest gastric metastasis, they are diverse in terms of location, size, number, shape, and presence or absence of bleeding, erosion or ulceration, which can imitate early gastric cancer to advanced gastric cancer, and can be located anywhere from the fundus to the antrum, even in the lesser curvature and posterior wall side of the remnant stomach.

Incipient gastric lesions are most commonly referred to as primary gastric cancers. A case that was diagnosed as early gastric cancer discovered gastric metastasis of breast cancer using endoscopic biopsies (32), and another case revealed that definitive diagnosis of metastatic breast cancer was confirmed after endoscopic mucosal resection of a presumed primary early gastric carcinoma (33).

It is difficult to consider gastric metastasis, particularly in the setting of a solitary gastric lesion. Some authors noted that solitary gastric metastases are more common than multiple lesions, and are mainly located in the middle or the upper third of the stomach (4).

Other authors showed that the most common type of gastric metastasis of breast cancer (73-83%) is linitis plastica (34-36).

Some authors think that patients with invasive lobular breast cancer of stomach should undergo screening EGD regularly to detect gastric metastases early (37,38).

Pathologic Diagnostic

A particular problem of gastric endoscopic biopsy occurs in patients with infiltrative gastric metastases. Initial biopsies in these cases can be normal in about 46–50% of the cases and demonstrate only discrete non-specific mucosal abnormalities indistinguishable from other tumours or benign disease, because invasion is often limited to the submucosa and seromuscular layers and is not detected by superficial biopsies, aspect that may delay the diagnosis for a while (39,40).

Thus, it is suggested to perform deep and extensive biopsies and to repeat them if negative, for obtaining representative material (41,42).

If biopsies obtained by repeated, standard or forced biopsy of the modified gastric mucosa do not contain enough malignant cells, biological material can be harvested by ultrasonographic guided fine needle aspiration (43,44).

Perhaps the most important aspect in the diagnosis of the disease is the obtaining the pathological material and of course the interpretation of the results of pathological exam. Some authors suggest that the histological features of gastric biopsies should be compared with those of the primary breast tumour in order to confirm the diagnosis (45).

An interesting situation was presented by many authors in patients with lobular invasive cancers and gastric metastasis, of which gastric biopsies contains signet ring shaped cells in pathologic examination and for this reason it was mistakenly thought that these patients might have a primary gastric cancer that is signet ring cell type gastric carcinomas (46).

Other authors have suggested that breast ring cell carcinoma may have some morphological distinctions from gastric or colic ring cell carcinoma, such as the presence of an intracytoplasmic, circumscribed, eosinophilic, central vacuole in lobular breast cancer, while other carcinomas have a globular mucoid inclusion that pushes the nucleus to the periphery of the cell (47).

A common situation in literature was that the initial pathologic diagnosis was diffuse-type gastric carcinoma, evaluated by pathologic exam of gastric endoscopic or ultra-
sonographic biopsy and the definitive diagnosis of metastatic breast cancer was confirmed after subtotal gastrectomy for a presumed primary gastric carcinoma and was obtained using a panel of specific immunohistochemically markers (48,49).

**Immunohistochemically and Molecular Diagnostic**

Detailed immunohistochemically analysis is the only relevant method for distinction between metastatic and primary gastric carcinoma, taking into account that metastases of lobular cancer generally keep approximately the same receptor status as the primary breast carcinoma (50-52).

The lobular cancer cells are usually, oestrogen receptor (ER) and progesterone receptor (PGR) positive, without overexpression or amplification of the human epidermal growth factor receptor 2 (HER-2/neu) gene.

Some authors reported that metastatic breast carcinoma is usually positive for cytokeratin 7 (CK7) (90%), gross cystic disease fluid protein 15 (GCDFP-15), carinoembryonic antigen (CEA), ER and PGR, and negative for cytokeratin 20 (CK20). Other studies outlined that CK20 demonstrates to be especially positive in gastric, colonic, pancreatic and in transitional cell carcinomas, while it is not noted in breast carcinomas (53-56).

ER and PRG receptors can be used to distinguish the metastatic breast cancer. First-generation antibodies against ER \( \beta \) are no longer used in standard practice. Using the second-generation antibodies against ER \( \alpha \) some authors concluded that ER \( \alpha \) expression can be used to diagnose gastric metastasis of breast cancer, because no primary gastric tumour expressed ER \( \alpha \).

Another immunohistochemically marker studied is E-cadherin, some authors observed that the lack of E-cadherin expression was related to metastatic lobular breast cancer (57,58). Around 90% of invasive lobular breast cancers present E-cadherin loss (59).

Some authors consider that loss of E-cadherin expression explains the unique histopathological features lobular breast cancer - these tumours are composed of relatively small, infiltrating and discohesive epithelial cells and do not form a well-defined mass, resembling the diffuse gastric cancer cells phenotype - a possible explanation of confusion with primary gastric cancer in the absence of immunohistochemical tests (60).

Another authors assumed that atypical pattern of metastases in invasive lobular cancers can be by virtue of loss of expression of epithelial E-cadherin (57), but metastasis of the digestive tract is a complex process and it is quite poorly explained at this time.

In the immunohistochemically evaluation, some authors reported that mammoglobulin and GCDFP-15 positive suggest metastases caused by breast cancer (4).

**Therapeutic Approach**

It appears that the occurrence of gastric metastases after lobular breast cancer would be related to adjuvant postoperative treatment.

Some author noticed that adjuvant systemic therapy with tamoxifen reduces the rate of relapse and improves survival both during and after 5 years of therapy in women with ER positive early stage breast cancer (61).

Some trials (NCIC CTG Ma17) recommended extending adjuvant hormonal therapy with an aromatase inhibitor (oestrogen synthetase), letrozole, for an additional 5 years after the first 5 years therapy with tamoxifen (62). A subsequent analysis of this trial showed that1–7 years after 5 years of tamoxifen treatment women still have a significant recurrence risk and this risk was markedly reduced by introducing delayed letrozole treatment up to 11 years and 16 years from diagnosis (61).

It further supports the idea of persistent or latent metastases occurring many years after the primary presentation of breast cancer. From the results of this trial, it can be concluded that despite the 5-year tamoxifen adjuvant treatment, women may continue to host latent clinical micro-metastases that are generally susceptible to antioestrogen therapy, regardless of the time of application of this therapy (61,62).
Meanwhile, long-term therapy, especially hormone-dependent breast cancer like lobular type, becomes a standard of care and the benefit to a small proportion of women at risk of late recurrence must be balanced against the risk of side-effects due to long-term treatment.

Improving the systemic therapies that are applied immediately after primary treatment of breast tumour is the safest way for long-term prophylaxis of metastases.

When gastric metastases of breast cancer appeared, it is crucial to obtain the right diagnosis in order to initiate the appropriate treatments - metastases treatments vs. treatment of a new tumour. Gastric metastasis of invasive lobular breast cancer represents evidence of systemic disease and systemic therapy, such as chemotherapy and/or hormonal therapy, rather than surgical resection is indicated (27,39,62,63).

In some cases or small series of patients with this disease, chemotherapy or endocrine therapy led to an evident palliative effect in only 30 - 50% of patients receiving systemic therapy with no evident difference in response rates between endocrine therapy and chemotherapy; the median survival of the patients from diagnosis of gastric metastases moment was 11-28 months (44,45,64,65,66).

Some authors recommended surgical treatment in the case of solitary gastric metastasis, followed by chemotherapy and hormonal therapy, surgical resection in these cases bringing survival benefit (67,68) or when gastric metastasis was the first symptom of lobular breast carcinoma with a long period of latency before presentation of the primary breast carcinoma (69,70).

At these patients, the role of surgery is usually limited, resection has been considered in selected cases. Palliative surgery has not been shown to improve overall survival (5).

Considering the stage of generalized disease, the current trend is to manage the complications of gastric metastasis in a minimally invasive manner: endoluminal stents for gastric outlet obstruction, endoscopic or endovascular therapy for tumoral bleeding (50,71).

Another authors suggest that the surgery should be reduced to palliative bypass in those patients where minimally invasive measures not succeed or patients who develop complications (5,39).

**Conclusion**

Given the low frequency of this type of tumour, latency in the development of gastric metastases, occurring especially after discontinuation of endocrine treatment are aspects that try to explain why confusion with a primary gastric tumour is possible. At the patients with a history of lobular breast cancer who have suspect gastric lesions we have to think about the possibility of distant metastasis. At these patients, obtaining pathologic material and biopsies interpretation can be a real challenge for getting a correct pathologic diagnosis, immunohistochemistry gives us definite diagnosis. The introduction of an endoscopic surveillance protocol for patients with lobular breast cancer could be a proposal for the detection of early gastric metastases allowing for appropriate therapy. An early diagnosis associated with the latest adjuvant systemic therapies and hormonal treatment, alone or in combination, may grant affected patients a remission with a reasonable survival rate and a reasonable quality of life.

**Conflicts of interest**

The authors declare that they have no conflicts of interest.

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