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# CASE REPORT

# A fatal gastric perforation secondary to ulcerated metastasis in undiagnosed breast cancer: pathological aspects and review of literature

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*Abstract*

The authors describe a fatal case of gastric perforation secondary to an ulcerated metastasis in a woman with undiagnosed breast cancer. The 48-year-old woman, with no significant medical history, presented with weight loss, persistent dyspepsia and pain in the epigastric and mesogastric region. She was treated by her primary care physician with proton-pump inhibitors and antispasmodics. The following day she was found dead at her home. External examination showed a tumefaction in the lateral region of her left breast, near the axilla. Autopsy revealed 1000 ml of turbid, light-brown peritoneal fluid in the abdominal cavity and a perforated gastric wall. Histological examination of the breast mass showed an infiltrating, poorly-differentiated breast carcinoma. Microscopical analysis of the stomach wall revealed a perforated metastatic gastric ulcer. Immunohistochemistry was required to confirm the neoplastic involvement of the stomach due to metastatic breast cancer.

*Keywords:* breast cancer, gastric metastasis, gastric perforation, fatal peritonitis

## INTRODUCTION

Breast cancer is the most common cancer in women, constituting the leading cause of cancer-related deaths worldwide.[1-3] Mortality rates in Europe, the US and Australia have registered a progressive decrease by virtue of early detection through mammography screening and improved treatment protocols.[4] The aetiology of breast cancer can be explained through a mechanism of differentiation and proliferation of mammary epithelial cells mediated by hormonal factors:[5] tumor growth appears related to proliferative endocrine stimuli that breast epithelium undergoes over the course of years, combined with the progressive cumulative effects of DNA damage and epigenetic alterations with subsequent imbalance between the expression of oncogenes and tumour suppressor genes.

Timing of menarche and menopause are established risk factors inasmuch as breast cancer risk increases for every year younger at menarche and, independently, for every year older at menopause.[4] Correspondingly, the incidence is higher in women on hormone replacement therapy.[1,5-7] Family history has long been a known risk factor for breast cancer.[8] Although the majority of breast cancers are sporadic, a modest percentage can be linked to hereditary factors, among which are those determined by BRCA-1 and BRCA-2 gene mutations. Other apparent risk factors for breast cancer include obesity, a particularly fat-rich diet, high alcohol consumption and exposure to ionizing radiation.[1,9]

Breast cancers tend to be localized mainly in the upper outer quadrants. They can be divided into carcinoma *in situ* and invasive (or infiltrating) varieties. Depending on their origin, they can be further subdivided into ductal or lobular types, with both arising from the terminal duct lobular unit. As regards cytological features, there are two distinct *in situ* types, i.e. ductal carcinoma *in situ* (DCIS), representing the more common variety, and lobular carcinoma *in situ* (LCIS).[10-12] Historically, DCIS was further subclassified by morphology, giving rise to five well-known architectural subtypes: comedo, solid, cribriform, papillary and micropapillary. Invasive variants are a heterogeneous histological group comprising: infiltrating ductal carcinoma; infiltrating lobular carcinoma; invasive lobular plus some other type such as lobulo-ductal,

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ductulo-lobular; mucinous carcinoma; tubular carcinoma; medullary carcinoma and papillary carcinoma.[13] Among these, infiltrating ductal carcinoma (IDC) is the most common subtype and represents 70-80% of all invasive lesions.[14]

By molecular-receptor profiling, the latter cancer can be divided into luminal A (positive for oestrogen and progesterone receptors), luminal B (positive for hormone receptors and HER-2), human epithelial growth receptor type 2 (HER-2) positive, basal-like (negative for all markers) and the lastly identified claudin-low subtype.[15,16]

The stage of the disease and molecular profile as well as the hormonal and receptor status are the main factors that influence the choice of treatment among the available therapeutic options.

Approximately 10-15% of breast cancer patients develop metastatic disease within 3 years from the onset of the primary tumour.[17] The most common sites of metastasis are the bone, lungs, brain and liver.[18] However, less frequently metastases involve other organs as well.

## CASE REPORT

We report the case of a 48-year-old woman with no significant medical history and in apparently good health, who reported weight loss, persistent dyspepsia and pain in the epigastric and mesogastric region. She was treated by her primary care physician with proton pump inhibitors and antispasmodic drugs. Family history was negative for neoplastic diseases. The following day, she was found dead at her home. An autopsy was performed 36 hours later to ascertain the cause of death.

*Autopsy findings*

The woman's weight and height were 55 kg and 160 cm, respectively. External examination showed a tumefaction in the lateral region of the left breast, near the axilla (Fig. 1a). This mass was about 6 cm and had a hard consistency, with an overlying excoriated and ulcerated skin area.

The autopsy revealed 1000 ml of light-brown and turbid peritoneal fluid (Fig. 1b) in the subcostal region and between the stomach and pancreas. The peritoneum and the serosa were intensely hyperemic. Macroscopical examination highlighted a 1.5 cm oval perforation of the gastric serosa at the anterior wall of the stomach (Fig. 1c). It was surrounded by hard fibrinous tissue arranged in a radial pattern. The gastric mucosa presented a perforated ulcer in the region of the corpus, with a crater-like appearance, disintegration of superficial epithelium, and blackish margins (Fig. 1d).

The tail of the pancreas had a parenchymal subversion with fat necrosis and the presence of whitish semi-gelatinous material.

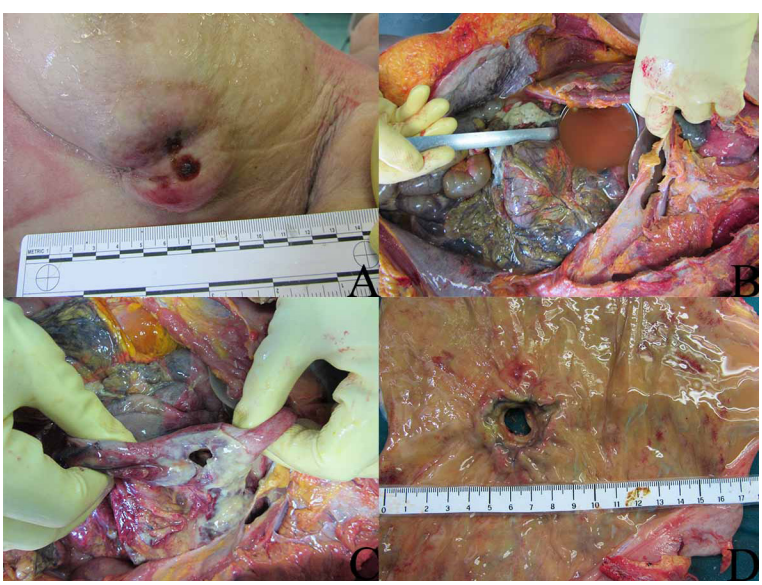


FIG.1: Autopsy findings. (A) Tumefaction in lateral region of the breast, in proximity to the axilla. (B) Peritoneal turbid and light-brown fluid in abdomen. (C) Oval perforation of the gastric serosa of the anterior wall of the stomach. (D) Perforated ulcer in the gastric mucosa, with crater-like appearance, disintegration of superficial epithelium, and blackish margins

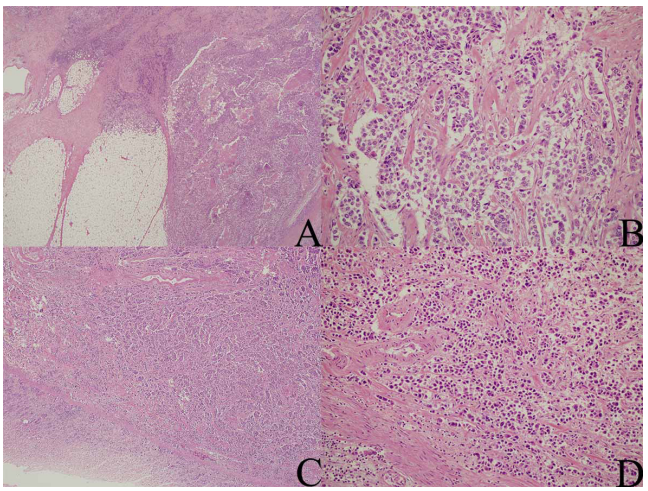


FIG. 2: Histological findings. (A-B) Poorly differentiated infiltrating breast carcinoma. The cancer was composed of large, pleomorphic cells with abundant cytoplasm, irregular nuclei, mitosis and variation in size and shape. H&E x2, H&E x20. (C-D) Neoplastic perforated gastric ulcer with soft tissue and pancreas infiltration. Tumour cells were arranged in nests with abundant eosinophilic cytoplasm. The mucosa presented no neoplastic alterations and the tumour developed within the submucosa. H&E x4, H&E x20

*Histology*

Histological examination of the breast lump stained with hematoxylin-eosin showed a poorly-differentiated infiltrating breast carcinoma (Fig. 2a). The cancer was composed of large, pleomorphic cells with abundant cytoplasm, irregular nuclei with marked variation in size and shape with evident mitotic activity (Fig. 2b). Moreover, microscopical analysis showed perineural and vascular neoplastic invasion. Immunohistochemistry revealed positivity for the E-cadherin and oestrogen receptor clone ER 88, while staining for progesterone receptor clone PR 88, CK7, CK20 and CDX2 were all negative. These data indicated a poorly differentiated infiltrating ductal breast carcinoma and they excluded a primary tumour of the stomach.

Histological examination of the stomach wall showed a perforated neoplastic gastric ulcer with soft tissue and pancreatic infiltration (Fig. 2c). Tumour cells were arranged in nests with abundant eosinophilic cytoplasm (Fig. 2d). The mucosa presented no neoplastic alterations whereas the tumour involved the submucosa. Immunohistochemical findings of the gastric tumour (Cadherin positivity, oestrogen receptor clone ER 88 positivity, and progesterone receptor clone PR 88, CK7, CK20, CDX2 negativity) confirmed the metastatic involvement of the stomach due to breast cancer (Figs. 3-5).

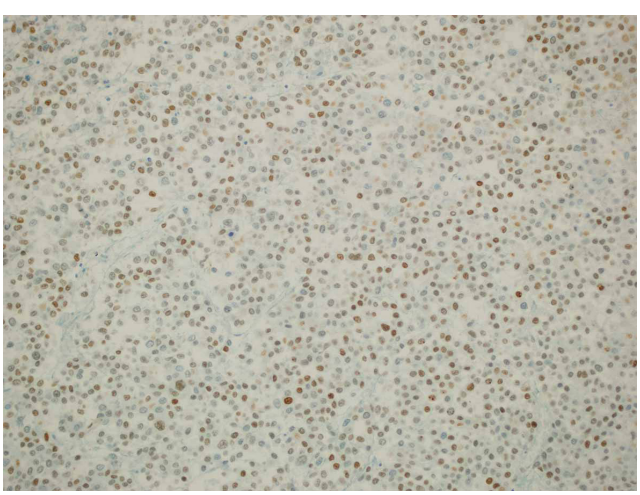

FIG. 3: Immunohistochemical findings. Metastatic lesion in the stomach: Positive staining for oestrogen receptor clone ER 88 confirmed the metastatic involvement of the stomach due to breast cancer. x20

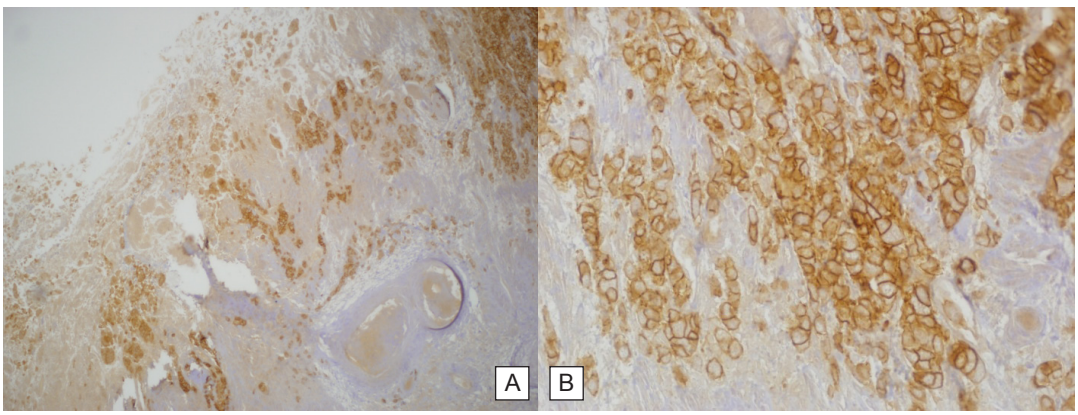


FIG. 4: Immunohistochemical findings. Metastatic lesion in the stomach: Positive staining for E-cadherin showed a ductal type. A x4. B x40

The histological analysis showed no other pathological findings.

On the basis of the macroscopic, histological and immunohistochemical results, the death was attributed to terminal cardiorespiratory failure developing as a complication of acute peritonitis from perforated gastric metastasis of primary undiagnosed breast cancer.

## DISCUSSION

Metastatic disease, i.e. the dissemination of tumour cells from the primary site to a distant location and the establishment of a new cancer growth, is responsible for the vast majority of deaths resulting from breast cancer.[19]

The mechanisms of metastasis in breast cancer include a cascade of steps. Failure of even one of these sequential processes determines its arrest.[20] Local invasion of surrounding tissues and diffusion via the bloodstream and lymph channels represent the initial phases of the metastatic process. Subsequently, circulating tumour cells adhere to capillary endothelium of target organ, and, upon extravasation, adhere to the basal membrane, thus invading the stroma/parenchyma where they proliferate and promote angiogenesis.[21] The growth of metastases and their spread are made possible by eluding the immune response and evading apoptosis, i.e. programmed cell death.[22]

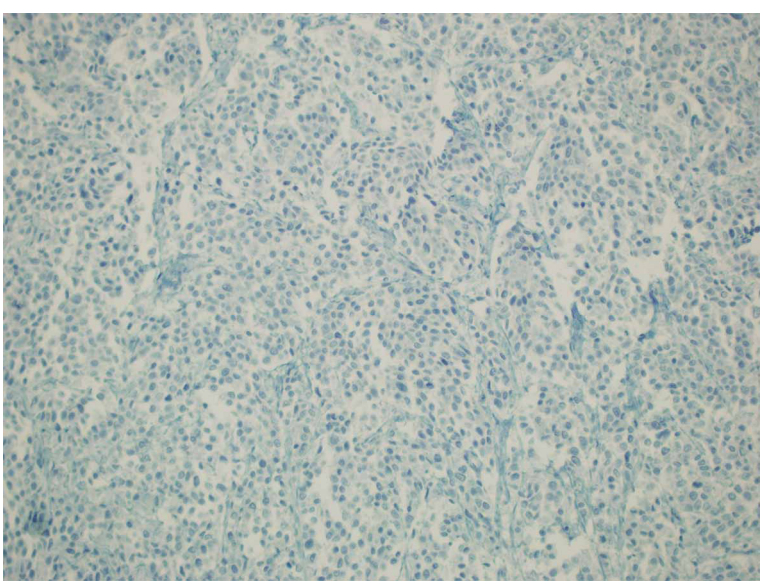

FIG. 5: Immunohistochemical findings. Metastatic lesion in the stomach: Negative staining for CK20 confirmed a metastatic cancer. x20

Cadherins are a class of transmembrane proteins that not only mediate cell-cell adhesion, crucial to tissue morphogenesis and homeostasis, but also play a key role in the metastatic process of breast cancer, particularly in the early phases characterized by invasion of the extracellular matrix (ECM).[23] A partial loss of E-cadherin expression is associated with accelerated progression to metastatic disease, since this protein mediates adhesion among epithelial cells.[21,24]

The greater metastatic tendency of lobular carcinoma appears correlated with mutations of E-cadherin genes, which determine their reduced functioning.[21]

The adhesion of tumour cells to the extracellular matrix occurs via integrin pathways.[25] The degradation of ECM, a prerequisite of tumour invasion, is mediated by matrix metalloproteinases, heparinase, β-glucuronidase and urokinase plasminogen activator.[26]

Subsequently, upon entering the blood stream or lymph channels, neoplastic cells migrate as circulating tumour microemboli.[21]

In order to reach the target organ and proliferate, the presence of a favorable microenvironment is necessary.[27] In this regard, it is assumed that tissue macrophages may influence tumour angiogenesis, migration and invasion of distant organs.[21,28,29]

According to study findings[30] the induction of metalloproteinase 9 in pulmonary endothelium and macrophages facilitates metastatic invasion of the lung. Indeed, chemokines are involved in the tumour homing phenomenon, favouring the preferential invasion in particular districts. In fact, lung, liver, bone marrow and lymph nodes, which are common sites of metastatic breast cancer, all have high levels of CXCR4 and CXCL12 expression.[21,31]

*Vice versa*, the low levels of these molecules in the gastrointestinal (GI) tract account for its relative rarity as a site of breast cancer metastasis.[32] Nevertheless, some studies have shown a predominance of infiltrating lobular carcinoma with GI involvement.[33] In fact, in a case series reported by Taal *et al*[34] 83% of gastric metastases consisted of the infiltrating lobular variant. Pectasides *et al*[35] reported 8 cases of gastrointestinal metastases from breast cancer, in which almost all were infiltrating lobular carcinomas. On the contrary, invasive ductal carcinoma is more frequently associated with spread to liver, lungs and brain.

Gastric involvement is extremely rare. While some authors have reported an incidence of about 0.3%[36,37], other studies have observed an incidence of 2-18%.[38-40] In general, gastric involvement occurs after many years of disease.

The clinical presentation of gastric metastases of breast cancer is often one of non-specific symptoms, with anorexia, dyspepsia, epigastric pain and vomiting.

Oftentimes metastatic gastric cancer mimics primary cancer of the stomach, making it essential to include both in the differential diagnosis, which requires macroscopical evaluation, histology and immunohistochemistry. Metastatic disease mainly presents as a diffuse linitis plastica-like infiltration, due to extensive infiltration of serosal, muscular and submucosal layers. This leads to an intense fibrotic reaction typical of linitis plastica with rigidity, wall thickening with reduced peristalsis. Rarely, it may present a nodular or ulcerated pattern.[41,42]

Histological criteria are of value in differentiating primary gastric lesions from breast cancer metastases. In particular, primary tumours predominantly involve the mucosa, while metastatic disease primarily affects submucosal layers.

Occasionally lobular histology may have a signet ring morphology and spread within the mucosa, thus mimicking gastric adenocarcinoma.[40,41]

Classically, signet ring cells are characterized by the presence of an eccentric nucleus and abundant, clear cytoplasm filled with large acidic mucin vacuoles.[43] In the case of breast carcinoma metastasis, these cells may have different cytological features consisting in a large intracytoplasmic vacuole with eosinophilic inclusions.[35]

Immunohistochemical analysis offers valuable support and in some cases proves to be the single most useful approach to the pathological diagnosis. Positivity for oestrogen (ER) and progesterone (PR) receptors is highly indicative of breast carcinoma metastasis. According to some studies,[44] no primary gastric cancer expresses ER. Therefore, oestrogen receptor positivity represents a valid and reliable tool in the differential diagnosis of gastric metastases and breast cancer. CK20 is a marker present in the stomach, colon, pancreas, but negative in breast cancer.[45] Thus CK20, as well as CDX2, a marker of intestinal differentiation,[46,47] is useful to confirm the diagnosis.

In the literature, there are few reported cases

of gastric metastasis as the first manifestation of breast carcinoma.[43,48] Furthermore, we conducted a literature search which produced no results of fatal perforated malignant gastric ulcer in undiagnosed breast cancer, highlighting the uniqueness of the case presented herein.

The fact that this case of advanced-stage breast cancer, with its extensive skin involvement, went completely unnoticed at her physician office visit and physical examination is also surprising. In the case herein described, the correct differential diagnosis relied on an accurate histological and immunohistochemical analysis. The finding of a tumour originating in the submucosa together with the lack of any mucosal layer involvement lent support to a diagnosis of metastatic disease. Immunohistochemistry then proved decisive: oestrogen receptor positivity and negativity for CK20 and CDX2 confirmed the metastatic nature. The morphology and positivity for E-cadherin corroborated a ductal type of carcinoma.

***Conclusion***

Although rare, gastric metastases from breast cancer do occur. The oncologist should consider this possibility whenever a patient develops symptoms of a gastrointestinal nature. From a pathological point of view a correct differential diagnosis is enabled through an accurate histological study and especially via immunohistochemistry. The positivity for hormone receptors and negativity for intestinal markers confirms the mammary origin. Finally, this case report also highlights the importance of taking a detailed patient history and performing a thorough physical examination whenever there are persistent symptoms and the clinical picture appears ambiguous and indistinct.

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