Breast cancer is the most common malignant tumor and accounts for about 27% of all malignancies in women [1, 2]. Invasive lobular carcinoma accounts for 5–15% of all breast cancers. Infiltrating lobular carcinoma is often multicentric, bilateral, more commonly gives local relapse and distant metastases, and is increasingly being diagnosed in postmenopausal women. Synchronous occurrence of two tumors is rare – especially rare are cases of synchronous malignant epithelial and mesenchymal tumors. Takeuchi et al. [3] described synchronous lobular breast cancer and gastrointestinal stromal tumor (GIST) in a patient with neurofibromatosis type 1. Adim et al. [4] published a case of synchronous and metachronous occurrence of a gastrointestinal stromal tumor and accounts for about 27% of all malignancies in women [1, 2]. Invasive lobular carcinoma accounts for 5–15% of all breast cancers. Infiltrating lobular carcinoma is often multicentric, bilateral, more commonly gives local relapse and distant metastases, and is increasingly being diagnosed in postmenopausal women. Synchronous occurrence of two tumors is rare – especially rare are cases of synchronous malignant epithelial and mesenchymal tumors. Takeuchi et al. [3] described synchronous lobular breast cancer and gastrointestinal stromal tumor (GIST) in a patient with neurofibromatosis type 1. Adim et al. [4] published a case of synchronous and metachronous occurrence of a gastrointestinal stromal tumor and the epithelial component was morphologically and immunohistochemically identical to the diagnosed primary breast cancer. Because of all this, the nodal tumor mass was interpreted as a primary gastrointestinal stromal tumor of the small intestine, in which the deposit of metastatic ductal breast carcinoma was observed.

**Conclusion**

Metastases of breast cancer in organs of the gastrointestinal tract are encountered rarely, mainly in the terminal stage of the disease. In available literature, a case of metastasis of breast cancer (metastasis of malignant epithelial tumors) in gastrointestinal stromal tumor has not been found.

**Keywords:** breast cancer; gastrointestinal stromal tumor; metastasis

**INTRODUCTION**

Metastases of breast cancer in the GIT can be clinically manifested as obstruction, bleeding, and often mimic a primary carcinoma [2]. Metastasis of breast cancer in the GIT are very rare. Borst and Ingold [7] followed 2,604 subjects for 18 years and found metastases in 17 patients (less than 1%). The analysis of Mourra et al. [8] showed that out of 35 patients with verified metastatic disease in the colon and rectum, in 17 cases the metastasis of breast cancer was present, which is almost half of all metastases that were analyzed by these authors.

Metastases of breast cancer in the GIT and peritoneum are an important differential diagnostic problem. Morphologically, they can mimic primary cancers localized in the GIT or peritoneum (mesothelioma). In some cases, metastases of breast cancer in the GIT may occur after several years (more than ten years), and the primary breast cancer sometimes becomes forgotten [1, 9]. All of the above may lead to the misinterpretation of cancer as primary cancer in the GIT [9].

We report a case of a patient with primary, synchronous bilateral breast cancer, which after five years of follow-up gave metastases to the lungs, bones, and peritoneum, and metastases of breast cancer in the GIT. After five years of follow-up, metastases to the lungs, bones, and peritoneum, and metastases of breast cancer were present.
CASE REPORT

A 57-year-old female patient had been diagnosed with a bilateral synchronous breast cancer five years previously. In the treatment of cancer of the right breast, the patient underwent mastectomy with dissection of axillary lymph nodes. Invasive ductal carcinoma of the breast (no special type – NST), grade 2, pT2N3aM0 was diagnosed (Figure 1.A). Immunohistochemical analysis of invasive components of the tumor revealed that the tumor had a positive staining for the estrogen receptor alpha (ER) and negative staining for the progesterone protein receptor (PR) and receptor of epidermal growth factor 2 (HER2). In the treatment of tumor of the left breast, the patient underwent a modified mastectomy. Analysis indicated the presence of invasive ductal carcinoma (NST), grade 2, pT1cN1aM0 (Figure 1.B). Immunohistochmically, the tumor of the left breast had the same characteristics as the tumor of the right breast. The patient received six cycles of chemotherapy. After chemotherapy, the patient received radiotherapy of both axillary regions and right pectoral region, followed by hormone therapy with tamoxifen.

Two years after the first surgery, a local relapse in the right pectoral region was confirmed, 7 × 5 mm in size, which was surgically removed and histologically identified as a relapse of the previous disease. The patient refused a specific oncologic therapy. Three years after the diagnosis of tumors in both breasts, further progression of the disease was found. Metastases were verified in both lungs and vertebrae. The patient still refused a specific oncological treatment.

Five years after the diagnosis of bilateral breast tumor, the patient was hospitalized with the clinical picture of acute ileus. A laparotomy was performed, which revealed the presence of masses in the small intestine (jejenum) and the mesentery. The two masses were resected.

One mass was located in the small intestine (jejenum) and was resected with a part of the small intestine in the length of 3.6 cm. On the opposite side of the mesentery (antimesenterically), a nodal tumor mass was present, with smooth surface and 4.5 × 3 × 2.5 cm in size. On the section, the nodal tumor mass was largely a solid, homogenous structure, whitish, and to a lesser extent cystic, brown and black. The mucosa of the small intestine over the nodal tumor mass was not changed (Figure 2). Histologically, the nodal tumor mass was located in the muscle and subserous layer of the wall of the small intestine and made of a mixed population of cells (mesenchymal and epithelial). The dominant component of the tumor (about 80%) was mesenchymal (Figure 3). Mesenchymal component of the nodal tumor mass was made up of uniform spindle cells with oval nuclei, granular chromatin, and eosinophilic cytoplasm. Mitotic figures were rare (3/50 HPF). The mesenchymal component of the tumor was immunohistochemically positive for the following antibodies: vimentin, CD117, CD34, Ki-67 (nuclear positivity was present in about 2% of the mesenchymal component of the tumor) (Figure 4). The epithelial component of the tumor was diffusely mixed with mesenchymal component and built of solid, trabecular, cribriform, atypical adenoid and tubular formations. The cell population had a moderate degree of polymorphism, oval nuclei, and eosinophilic cytoplasm. In the lumen of adenoid and tubular formations, there was an eosinophilic content. Mitotic figures in the epithelial component of the tumor were rare (3/10 HPF). In the stroma, there were lymphocytes, histiocytes, and areas of bleeding. Epithelial component made approximately 20% of the tumor. Immunohistochmically, the epithelial component was positive for the following antibodies: CK (AE1/AE3), CK7, CEA (m), ER, GCDFP15, and E-cadherin (Figure 5). The negative reaction of both components of the tumor was found for the following antibodies: CK (HMW), 5/6 CK, CK20, CDX2, ESA (BerEp4), calretinin, chromogranin A, synaptophysin, and CD56. The nodal tumor mass was well circumscribed, with expansive growth, and on the surface there was a complete connective tissue pseudocapsule. In the vicinity of the described tumor, the small intestine did not show morphological changes. Based on the morphological and immunohistochemical characteristics, the nodal tumor mass localized in the small intestine was interpreted as a primary GIST of the small intestine, low risk, in which the previously diagnosed ductal breast cancer metastasized.

The second tumor change that was removed during the same procedure was localized in the mesentery. Histologically, it was interpreted as a metastatic deposit of previously diagnosed ductal breast cancer.
DISCUSSION

Gastrointestinal stromal tumors are usually solitary tumors in patients aged 50 to 60 years, with no association to tumors of another histogenetic origin. Associated occurrence of GIST and other tumors is present in patients with syndromes such as neurofibromatosis type 1, Carney triad, and familial GIST. The association of GIST with other tumors, in patients who do not have the aforementioned syndromes, is rare and reports in the literature vary from 4.5% to 33% [10]. Gonçalves et al. [10] followed 101 patients with GIST and established the existence of other tumors (other than GIST) in 14 patients (13.8% of cases). In this study, there was a case of association of GIST and ductal breast cancer. In most cases, GIST was less than 5 cm in size and had a low or very low malignant potential. It is diagnosed accidentally during surgery or follow-up of other malignancies. In the study by Gonçalves et al. [10], there was one case of a relation between GIST and ductal breast cancer. The most common localization of the coexistence of GIST and other tumors are stomach and colon [11]. Coincidence is certainly not the only explanation of the phenomena of synchronous and metachronous neoplasms with GIST. Possible reasons may be the presence of tumor syndromes, new genetic changes, and exposure to carcinogenic agents. A significant number of authors concluded that there is a greater incidence of gastrointestinal tumors in patients with GIST than in the general population [10]. AbdullGaffar [12] in his research established the relation between GIST and tumors out of the gastrointestinal system. The study included 21 patient, four of which (24% of cases) had GIST and another tumor outside the GIT.

Agaimy et al. [11] analyzed 4,813 cases and found the synchronous or metachronous presence of other malignancies in 486 cases. They showed the association of most types of GIST with malignancies localized in the GIT (47%). Lymphoma/leukemia and breast cancer were associated with GIST in 7% of cases each, cancer of the prostate was associated with GIST in 9% of the cases, kidney cancer in 6%, cancers of lungs and female genital system in 5% each, carcinoid and soft tissue tumors including osteosarcoma in 3% each, melanoma in 2%, and seminoma were associated with GIST in 1% of the cases. Similar results were obtained by Adim et al. [4], who studied 78 cases and found another malignancy in 13 patients (16.6% of cases).

Takeuchi et al. [3] presented a patient who suffered from neurofibromatosis type 1 and who had been diagnosed with invasive ductal carcinoma of the left breast, and after seven years with invasive lobular carcinoma of the right breast and synchronous GIST of the small intes-
tine. In the present case, metastases of breast cancer in the peritoneal cavity and GIST were not found.

The incidence of breast cancer metastases in organs of the GIT is rare. In the literature, the frequency is up to 0.34%. McLemor et al. [13] have identified the presence of metastases in the GIT in 41 patients, out of the total number of 12,001 patients. Invasive lobular carcinomas more often give metastases to the GIT compared to the ductal carcinoma [13]. Metastases of breast cancer in the GIT may occur many years (usually between five and 20 years) after primarily diagnosed breast cancer. The authors note that metastases occur after an average of seven years. The most common localization of metastatic breast cancer in the GIT are stomach and small intestine, rarely the colon [13]. Metastases of breast cancer in the GIT are usually associated with metastases in other organs (up to 90% of cases) [13]. Mourra et al. [8] analyzed tumor metastases in colon and rectum. The total number of analyzed cases was 35, and in as much as 48.6% of the cases it was a metastatic breast cancer. The cause of metastatic breast cancer in organs of the GIT is not entirely clear. A possible reason is a certain tropism of tumor cells of lobular or ductal carcinoma. The synchronous or metachronous occurrence of GIST and various other tumors is not clear. It is possible that there is a common pathogenesis or a cause, especially in women. It is necessary to conduct more clinical, epidemiological, and genetic studies to determine the clinical significance of the association among GIST and extraintestinal tumors.

In the literature, we did not find any information about the presence of a synchronous invasive ductal cancer, metachronous GIST in the small intestine, and the presence of metastatic ductal carcinoma in GIST tumor. In our patient, five years after the diagnosis of bilateral, synchronous breast cancer the presence of metastases in the lungs, bones, and organs of the GIT (mesentery) was showed. At the same time, GIST of the small intestine (jejunum) was diagnosed, in which the histological and immunohistochemical analysis showed the presence of ductal carcinoma of the breast. Due to the presence of metastasis of epithelial tumor (ductal breast cancer) in a malignant mesenchymal tumor (GIST), this case is unique.

Miller et al. [14] described the case of a patient with a synchronously diagnosed adenocarcinoma of the colon and metastatic lobular breast carcinoma in the colon and small intestine. Colon adenocarcinoma was localized in the sigmoid colon. Strictures in the small and large intestine, including the sigmoid part, were occupied by the tumor tissue with the histological image consistent with lobular breast cancer. Breast cancer had not been previously diagnosed. The authors point out that this is the only case in the available literature of coexistence of colon adenocarcinoma and metastatic lobular breast cancer in the same part.
of the colon, where breast cancer had not been diagnosed previously [14]. The authors described the presence of one tumor next to another (coexistence) and did not describe the presence of metastatic deposits of lobular carcinoma of the breast in the primary adenocarcinoma of the colon.

Macías-García et al. [15] were the first to describe a collision of GIST and prostate cancer. The authors described a high-risk GIST of the spindle cell variant that originated in the anterior rectal wall and that exhibited perirectal extension and wide infiltration of the adjacent peripheral prostate lobules, as well as a prostatic acinar adenocarcinoma.

The diagnosis of metastatic breast cancer in the GIT can be difficult due to several reasons. The first reason is a long period from the diagnosis of the primary breast tumor (usually more than five years), which can lead to the neglect of the primary disease. The second reason is the clinical presentation of the disease, which can mimic a disease of the GIT. Clinically, it can be manifested as the primary tumor, followed by abdominal pain, anorexia, vomiting, bleeding, obstruction, perforation, etc. The following possible reasons are difficulties in obtaining appropriate material: usually, the tumors are located in the subserous and muscle layer of the wall and are inaccessible to endoscopic sampling, as well as the morphological similarities with primary tumors localized in the GIT [8, 16, 17, 18]. In order to overcome the difficulties in differentiating, it is necessary for all participants in the diagnostic and the treatment team to have information about previous interventions and diagnosed diseases. It is necessary to have information on their progress and to have the possibility to access the previous diagnostic procedures (radiological, histological) that can be compared to the morphological, immunophenotypic image of the previously diagnosed disease with samples that are subsequently obtained. In this way, the possibility of misinterpretation of tumor process should be minimized.

All of the above has helped us in the differentiation of the nodal tumor mass in the small intestine, which was morphologically composed of two malignant components (epithelial and mesenchymal). The mesenchymal component had histological and immunophenotypic characteristics of GIST, while the epithelial one was morphologically and immunohistochemically identical to the primary diagnosed breast cancers. The nodal tumor mass was interpreted as a primary GIST of the small intestine where the deposit of ductal metastatic breast cancer was observed.

The prognosis of survival in cases of metastatic breast cancer in the GIT is poor and is less than two years [5, 17]. Appropriate systemic therapeutic approach for metastatic breast cancer in the GIT has a positive effect. Total therapeutic response to the systemic therapy is between 32% and 53%. Systemic therapy has a beneficial effect on survival, while surgical treatment has no significant effect on survival [18].
REFERENCES


