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Case Report / Приказ случаја

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Jejunal tumor made of primary gastrointestinal stromal tumor and metastatic breast carcinoma – an extremely rare case

Тумор јејунума сграђен од примарног гастроинтестиналног стромалног тумора и метастатског карцинома дојке – изузетно редак случај

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SUMMARY

Introduction The occurrence of synchronous or metachronous malignant epithelial and mesenchymal tumors is rare. Infiltrating ductal breast cancer rarely produces metastasis in the gastrointestinal tract, and when it does it represents a significant differential diagnostic problem. Morphologically they can mimic primary cancers localized in the gastrointestinal tract or peritoneum.

Case outline In this paper we showed a female patient with primary, synchronous bilateral breast cancer, which after five years of follow-up had given metastases to the lungs, bones, peritoneum and mesentery, and in a node localized in the small intestine. The node was built of two malignant components, mesenchymal and epithelial. Mesenchy-mal component had histologic and immunophenotypic characteristics of gastrointestinal stromal tumor (GIST) and 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 GIST of the small intestine, in which the deposit of metastatic ductal breast carcinoma was observed.

Conclusion Metastasis 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 in GIST has not been found.

Keywords: gastrointestinal stromal tumor; breast cancer; metastasis.

САЖЕТАК

Увод Појава синхроних или метахроних малигних епителних и мезенхимних тумора је ретка. Инфилтративни дуктални карцином дојке ретко даје метастазе у гастроинтестиналном тракту, а кад се појаве представљају значајан диференцијално дијагностички проблем. Морфолошки могу имитирати примарне карциноме локализоване у гастроинтестиналном тракту или перитонеуму.

Приказ болесника Приказана је болесница са примарним, синхроним билатералним карциномом дојке, који је након петогодишњег праћења дао метастазе у плућа, кости, перитонеум, мезентеријум и у чвор локализован у танком цријеву. Чвор је грађен од двије малигне компоненте мезенхимне и епителне. Мезенхимна компонента је хистолошких и имунофенотипских карактеристика гастроинтестналног стромалног тумора (ГИСТ), а епителна компонента је морфолошки и имунохистохемијски идентична примарно дијагностикованим карциномима дојке. Због тога је туморски чвор интерпретиран као примарни ГИСТ танког црева, у којем је уочен метастатски депозит дукталног карцинома дојке.

Закључак Метастазе карцинома дојке у органе гастроинтестиналног тракта се срећу ретко, углавном у терминалним стадијуму болести. Метастаза карцинома дојке у ГИСТ у доступној литератури није описана.

Кључне ријечи: гастроинтестинални стромални тумор; карцином дојке; метастаза

INTRODUCTION

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% to 15% of all breast cancers. Infiltrating lobular carcinoma is often multicentric, bilateral, more common gives local recidives and distant metastases, and is increasingly being diagnosed in postmenopausal women. Synchronous occurrence of two tumors is rare- especially are rare cases of synchronous malignant epithelial and mesenchymal tumors. Takeuchi and co-authors described synchronous lobular breast cancer and gastrointestinal stromal tumor (GIST) in a patient with neurofibromatosis type 1 [3]. Adim and colleagues published a case of synchronous and metachronous occurrence of GIST with other malignant tumors in the gastrointestinal tract (GIT). They found that GIST could be synchronously or metachronously present with malignancies out of the GIT, most commonly in the breast [4]. Afif and colleagues described a rare synchronous bilateral breast cancer and gastric GIST [5]. Infiltrating

ductal carcinoma of the breast gives metastases to the lungs, bone and liver, and metastases of infiltrating lobular carcinoma frequently involve GIT, the peritoneal surface and retroperitoneum [2]. Isolated adrenal metastases originating from invasive ductal carcinoma of the breast are extremely rare [6]. Metastases in the GIT can be clinically manifested as obstruction, bleeding, and often mimic a primary carcinoma [2]. Metastasis of breast cancer in GIT are very rare. Borst and Ingold followed 2 604 subjects for 18 years and found metastases in 17 patients (less than 1%) [7]. The analysis of Mourre and associates 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 [8].

Metastases of breast cancer in 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 GIT may occur after several years (more than ten years), and sometimes the primary breast cancer gets forgotten [1,9]. All of the above may lead to 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 metachronous (after five years) GIST in the small intestine. We particularly emphasize that, at the same time, GIST of the small intestine and metastasis of breast cancer in GIST were present.

CASE REPORT

A 57- year- old female patient has been diagnosed with a bilateral synchronous breast cancer five years ago. 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

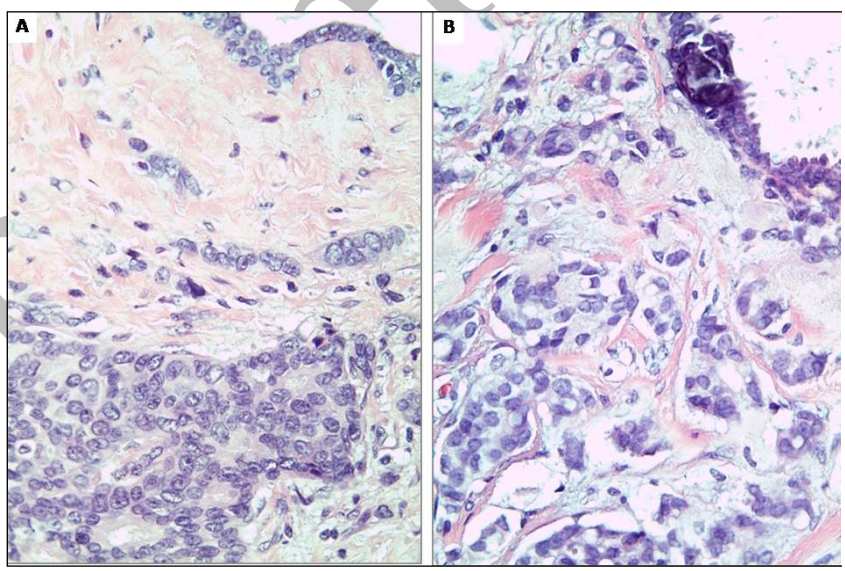

Figure 1. Bilateral ductal breast cancer - A: Microscopic image of ductal cancer in the right breast, B: Microscopic image of ductal cancer in the left breast, HE x400.

the treatment of tumor of the left breast, patient underwent a modified mastectomy. Analysis indicated the presence of invasive ductal carcinoma (NST), grade 2, pT1cN1aM0 (Figure 1.B). Immunohistochemicaly, 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 recidive in the right pectoral region was confirmed, 7x5 mm in size, which was surgically removed and histologically identified as a recidive of previous disease. The patient refused a specific oncologic therapy. Three years after the diagnosis of tumors in both breasts the 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 diagnosis of a 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 (jejunum) and the mesentery. Two masses were resected.

One mass was located in the small intestine (jejunum) 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 size of 4.5x3x2.5 cm. 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 has not been changed (Figure 2). Histologically, the nodal tumor mass was located in the muscle and subserous layer of the wall of

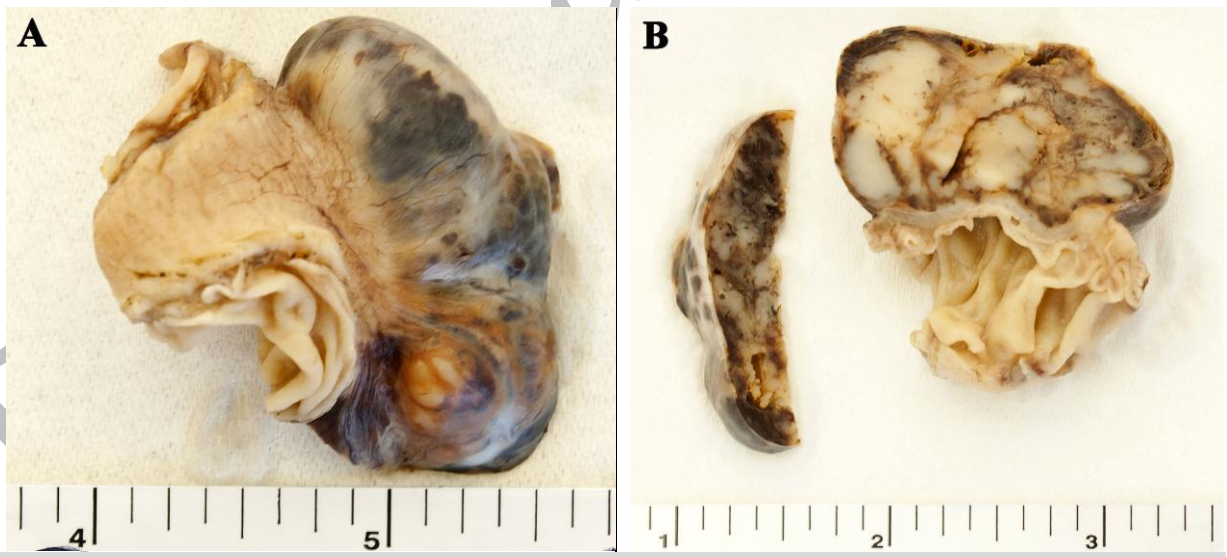

Figure 2. The macrocopic appearance of resected nodal tumor mass localized in the small intestine (jejunum)– A. External surface of the node; B: Appearance on node section.

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 built by uniform spindle cells with oval nuclei, granular

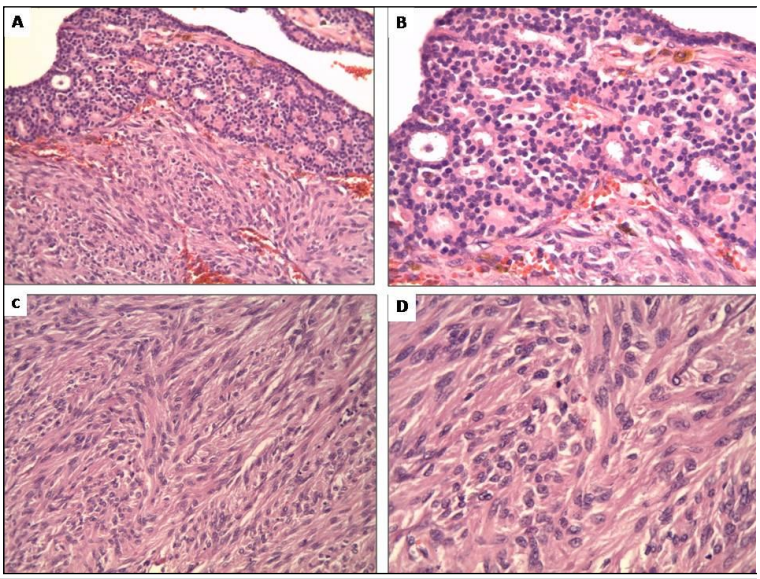

Figure 3. Histological image of the small intestine tumor, built by mesenchymal and epithelial component. A. In the upper part of the image there is an epithelial component of the tumor, and in the lower part, there is a mesenchymal component, HEx200; B. HEx400; C. Histologic appearance of mesenchymal component of the small intestine tumor, HEx200, D. HE×400.

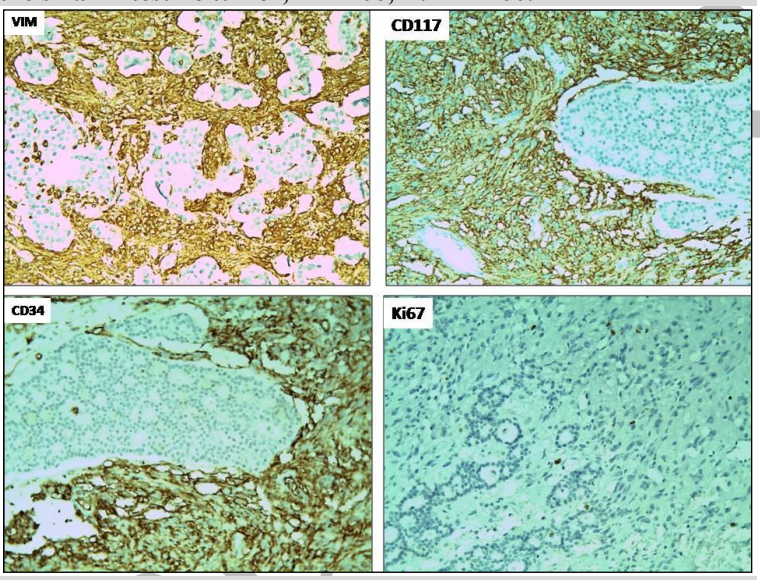

Figure 4. Immunohistochemical image of the small intestine tumor. Mesenchymal component is positive to vimentin, CD 117 and CD 34. Ki 67 positivity is seen in rare mesenchymal cells, x 200.

chromatin, and eosinophilic cytoplasm. Mitotic figures were rare (3/ 50HPF). 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. Tumor cells 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 (3/10HPF). In the stroma, there were lymphocytes, histiocytes, and areas of bleeding. Epithelial component made approximately 20 % of the tumor. Immunohistochemically epithelial component was positive for the following antibodies: CK (AE1/AE3), CK7, CEA (m), ER, GCDFP 15 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, small intestine did not show morphological changes. Based on morphological and immunohistochemical characteristics, the nodal tumor mass localized in the small intestine was interpreted as a primary

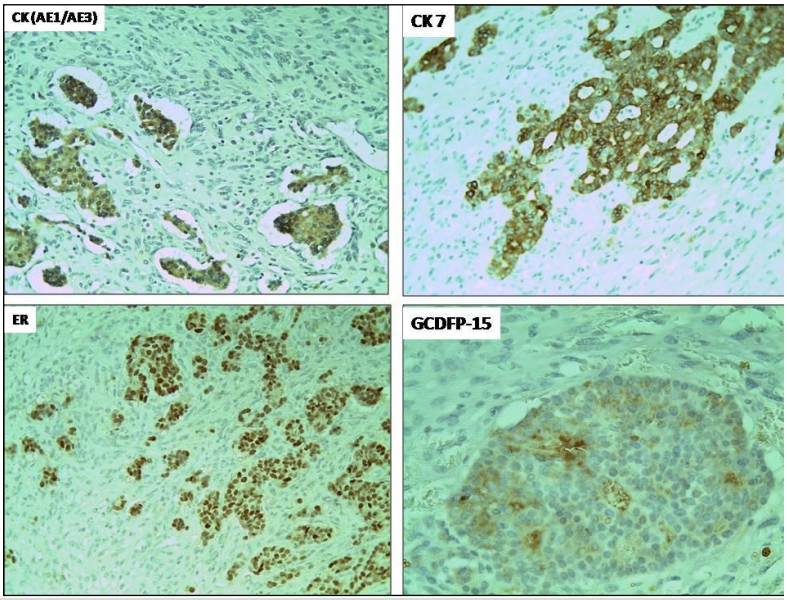

Figure 5. Immunohistochemical image of the small intestine tumor. Epithelial component of the tumor shows immunopositivity to cytokeratin (AE1/AE3), cytokeratin 7, ER and GCDFP-15. × 200.

GIST of the small intestine, low risk, in which the previously diagnosed ductal breast cancer metastasized.

The second tumour change that has been removed during the same procedure was localized in the mesentery. Histologically it was interpreted as a metastatic deposit of previously diagnosed 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, Cyrney 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]. Goncalves and colleagues followed 101 patients with GIST and in 14 patients (13.8% of cases), established the existence of other tumors (other than GIST). In this study, there was a case of association of GIST and ductal breast cancer. In most cases, GIST was less than 5 cm, and had a low or very low malignant potential. It is diagnosed accidentally during surgery or follow-up of other malignancies. In this study, there was one case of a relation between GIST and ductal breast cancer [10]. 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 in his research established the association among GIST and tumors out of the gastrointestinal system. The study included 21 patient, of which 4 (24% of cases) had a GIST and another tumor outside of the GIT [12].

Agimy and colleagues analyzed 4813 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 in 9%, kidney cancer in 6%, cancers of lungs and female genital system in 5% each, carcinoid and soft tissue tumors including osteosarcoma in 3 % each, 2% in melanoma and seminoma in 1% of the cases [11]. Similar results were obtained by Adim

and colleagues, who studied 78 cases and found another malignancy in 13 patients (16.6% of cases) [4].

Takeuchi and co-workers have presented a patient who suffered from neurofibromatosis type 1 and who has 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 intestine [3]. 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 and colleagues have identified the presence of metastases in the GIT in 41 patients, out of the total number of 12001 patients. Invasive lobular carcinomas more often give metastases to GIT compared to the ductal carcinoma [13]. Metastases of breast cancer in the GIT may occur many years after primarily diagnosed breast cancer (usually from 5 to 20 years). The authors note that metastases occur after an average of 7 years. The most common localization of metastatic breast cancer in the GIT are stomach and small intestine, rarely the colon [13]. Metastasis of breast cancer in the GIT are usually associated with metastases in other organs (up to 90% of cases) [13]. Mourra and colleagues analyzed tumor metastases in colon and rectum. The total number of analyzed cases was 35, and even in 48.6% of cases, it was a metastatic breast cancer [8]. The cause of metastatic breast cancer in organs of 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 gastrointestinal tract (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 and colleagues described the case of a patient with a synchronously diagnosed adenocarcinoma of the colon and metastatic lobular 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 has 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 has 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 and associates were the first to describe a collision 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 [15].

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 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 is necessary that all participants in diagnostic and treatment team 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 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). Mesenchymal component had histological and immunophenotypic characteristics of GIST, while 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 GIT is poor and is less than two years [5,17]. Appropriate systemic therapeutic approach for metastatic breast cancer in 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].

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