

DUODENAL AND COLONIC METASTASIS AS THE FIRST MANIFESTATION OF A MULTICENTRIC INVASIVE LOBULAR CARCINOMA OF THE BREAST

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Invasive lobular carcinoma (ILC) is the second most common breast cancer after invasive ductal carcinoma. The incidence of bilateral ILC of the breast varies from 6 to 38%, and most often it metastasizes to the lymph nodes, bones, lungs, pleura, liver and adrenals, but the tumour has the affinity to metastasize to the peritoneum, retroperitoneum and genitourinary system as well. Since ILCs rarely metastasize to the gastrointestinal tract, we are presenting in this report the case of a 58-year-old woman with bilateral lobular, multicentric breast cancer with gastrointestinal symptoms at initial presentation due to the presence of metastases in the duodenum and colon.

Based on the histological growth pattern and immunohistochemical characteristics of malignant cells in endoscopic biopsies of the duodenum and colon, and after gastroduodenoscopy and colonoscopy, a lobular carcinoma was suspected. Ultrasound and mammography of both breasts revealed numerous tumor nodules with malignant radiological features, up to 7 mm in size. A subcutaneous mastectomy was made with axillary lymph node dissection on the right side and reconstruction of both breasts with implantation of silicone prosthesis. The final diagnosis of invasive bilateral multicentric breast cancer was made based on the operative biopsies.

The reported case confirms the aggressive and unpredictable phenotype of this tumour. We should bear in mind that the presence of distant, GI tract metastases, usually causes nonspecific symptoms and signs, which significantly contributes to delayed diagnosis and consequently exacerbates the prognosis. *Acta Medica Medianae* 2016;55(4):60-65.

Key words: *invasive lobular carcinoma, distant metastasis, duodenum, colon*

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Introduction

Breast cancer is the most common malignant tumour and the leading cause of death from malignant disease in women. It is estimated that 521,900 women worldwide died from breast cancer in 2012. The incidence of breast cancer is particularly high in North America, Australia and Northern and Western Europe, moderate in Latin America, Central and Southern Europe, and low in

Asia and sub-Saharan Africa (1). The common standing in the literature is that breast cancer is a multifactorial disease that depends on the interplay of environmental, internal, genetic, hormonal and metabolic factors. Regarding this, it is usually emphasized that early menarche, late menopause and hormone therapy to prevent or maintain a pregnancy increases the risk of breast cancer (2-4). Other risk factors include genetic predisposition, age, obesity, harmful habits (alcohol, cigarettes), insufficient physical activity, ionizing radiation, stress, etc. (3-6).

Two major histomorphological types of breast cancer are invasive ductal carcinoma and invasive lobular carcinoma, with invasive ductal carcinoma as the most common type of breast cancer (2). Lobular cancers account for about 1% of all malignant tumours in women, by its frequency it is next to ductal carcinoma and it is found in 5-15% of breast cancer cases. Invasive lobular carcinomas most commonly metastasize to the lymph nodes, bones, lungs, pleura, liver, brain, and adrenals (7, 8). Since lobular breast carcinoma rarely metastasizes to the gastrointestinal tract, we are presenting in this report the case of

a woman with bilateral, lobular, multicentric breast cancer with metastases in the duodenum and the colon already at initial presentation.

Case report

The patient, a 58-year-old woman went to see her doctor because of anaemia, weight loss, nausea, dyspepsia and diarrhoea. The first problems began six months before the visit to the doctor. By the time she went to a gastroenterologist, CT scanning and abdominal ultrasound did not reveal any pathological changes. Osteolytic changes were found in the first vertebrae and the pelvis, so the differential diagnosis involved a haematological disease, followed by anaemia. Since gastrointestinal complaints prevailed in the clinical picture, after the examination by a gastroenterologist, with the clinical diagnosis of "chronic gastroduodenitis", the patient was asked to perform GI endoscopy and colonoscopy in order to exclude a gluten enteropathy.

In duodenal tissue samples, in the steep biopsies of the colon, in the lamina propria which was hypercellular, infiltrates were present made of smaller, atypical, and round cube-like tumor cells, in an one-cell-thick pattern (the "Indian file" formation) (Figure 1). Immunohistochemical analysis of tumor cells was done, with the expression of pancytokeratin (AE1/AE3), cytokeratin 7 (CK7), epithelial membrane antigen (EMA) and estrogen receptor (Figure 2, 3, 4). In tumor cells, the expression of vimentin and CD68 was not seen. On the basis of micromorphological images and immunohistochemical status, the diagnosis of a lobular breast cancer metastatic to the duodenum and colon was made. After the histopathological analysis, ultrasound examination and mammography of both breasts were carried out. In both breasts, several nodules with radiological characteristics of a malignancy, sized up to 6.5 mm were noticed. The patient was referred to the surgery, where the pathologist using the ex-tempore biopsy concluded that it was the case of malignancy in both breasts. We performed bilateral subcutaneous mastectomy with axillary lymph node dissection on the right side. Both breasts were then reconstructed with the placement of silicone endoprotheses. In the operational material from the right breast, a multifocal lobular carcinoma with tumour focus size from 3 to 7 mm was diagnosed. In the left breast, a multifocal lobular carcinoma with tumour focus size from 1 to 2 mm was diagnosed as well (Figure 5). Steroid receptors status was then established, as well as HER2 status. Estrogen receptors were very positive, and the expression of E-cadherin, progesterone receptors and Her2 were all negative.

In the axillary lymph nodes the following was established: status of "I and II level" lymph nodes to the right - in all 17 isolated lymph nodes, secondary deposits of the primary breast tumors were found. The size of the largest lymph node

was 13 mm. There was a perinodal infiltration of fatty tissue of axillary lymph nodes. Status of "le-

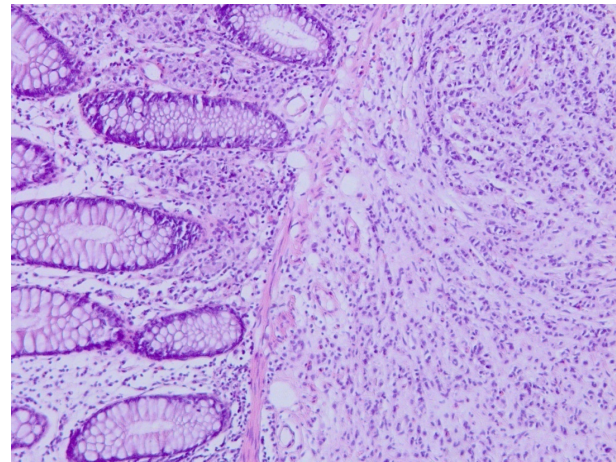


Figure 1. Infiltration of the lamina propria mucosa and submucosa of the colon tumor cells, the "Indian file" arrangement (HEEx100)

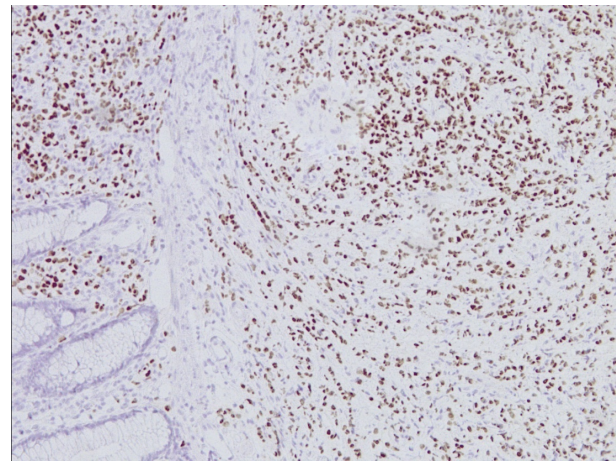


Figure 2. Infiltration of the lamina propria mucosa and submucosa of the colon tumor cells that is positive to estrogen receptors (IHHx100)

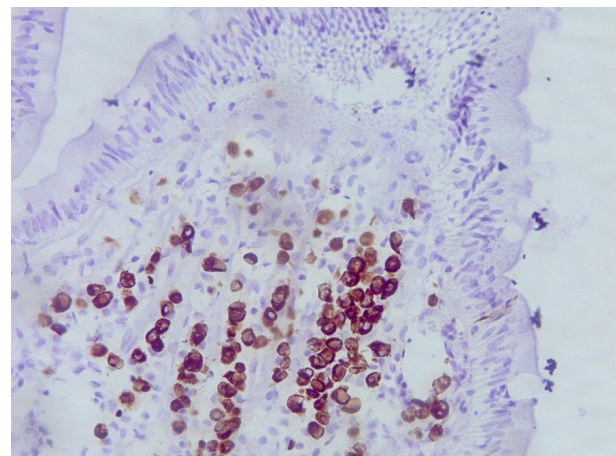


Figure 3. Tumor cells infiltrating the lamina propria of the small intestine mucosa positive to Cytokeratin 7 (IHHx200)

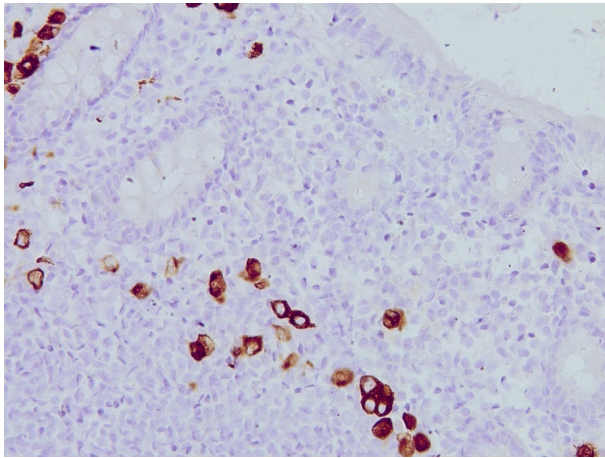


Figure 4. Tumor cells infiltrating the lamina propria of the colon mucosa positive for Cytokeratin 7 (IHHx200)

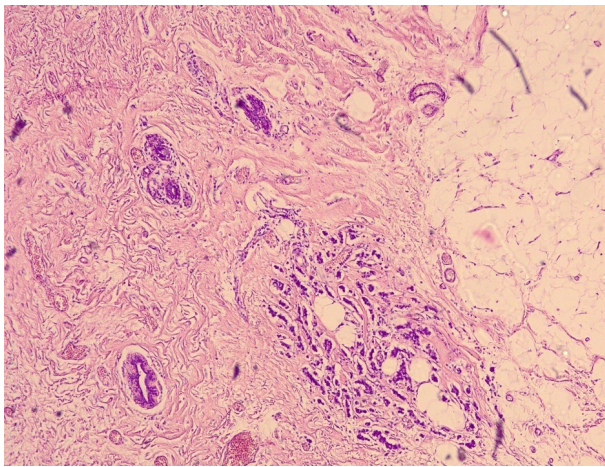


Figure 5. Focus of multicentric breast lobular carcinoma (HE, x40)

vel III" axillary lymph nodes - secondary deposits of the primary breast tumor were found in all 6 isolated lymph nodes. The size of the largest lymph node was 5 mm. There was a perinodal infiltration of fatty tissue of axillary lymph nodes.

Histopathological examination

The biopsy material obtained by gastro duodenoscopy and colonoscopy, as well as the operational material, after the subcutaneous mastectomy on both sides, were submitted to the Department of Pathology. After measuring and determining the dimensions, tissue samples were fixed in 10% neutral buffered formaldehyde, routinely processed and embedded in paraffin. Sections 3 to 4 μ m thick were made from the paraffin blocks, on which the routine haematoxylin-eosin method for histopathological verification was applied, as well as the immunohistochemical analysis.

The sample tissues used for immunohistochemical analysis were mounted on the highly adherent plates (SuperFrost) and then dried at 60°C in a thermostat for 24 hours. Then the sam-

ples were treated in PT Link (Dako, Glostrup, Denmark) (reagent: EnVision Flex Target Retrieval S006Flution High pH) for 10 min until a rise in temperature, followed by 20 min at a constant temperature of 98°C and then for 10 min in the cooling process. After the preparation of sample tissue in the PT link, further immunohistochemical staining was automated. The Autostainer Link 48 (Dako, Glostrup, Denmark) was used. Dako EnVision Flex system was used for the visualization: endogenous peroxidase blocking (for 10 min), application of primary antibody (for 30 minutes), use of detection systems (for 20 minutes) and chromogen (for 10 minutes). Primary antibodies Dako, Flex Ready to use were used, and as a chromogen the DAB to (diaminobenzene) was used. Contrasting the haematoxylin was done manually (from 3-5 min).

Discussion

Invasive breast cancer accounts for 22% of all malignant tumours in women. The second most common invasive malignant breast tumour is lobular carcinoma, the incidence of which is growing at an alarming rate in the last decades of the last, and at the beginning of this century. Studies conducted in the US between 1987 and 1999 indicated that the incidence of invasive lobular carcinoma in this period had increased by almost 65%, while in the same period the incidence of invasive ductal carcinoma had increased for 3% only (9). If one bears in mind the Dossus report the authors of which have recently shown that exposure to female sex hormones is in a stronger positive correlation with lobular than with ductal carcinoma (10), a higher incidence of lobular carcinoma in recent decades could be attributed to increased and/or uncontrolled use of combined hormone replacement therapy (8). There are observations of other authors that corroborate this theory that recent hormone replacement therapy with a lower concentration of estrogen in menopausal women, has led to a reduction in the incidence of breast cancer in some countries (4, 11). Regarding the genetic risk factors, it has been observed that the BRCA1 gene TP53 is predominantly associated with infiltrating ductal carcinoma, and BRCA2 mutations are associated with both histological type of cancer. It has been also found that invasive lobular carcinoma is the only histological type of breast cancer that is connected with mutations of CDH 1 gene family (10).

The incidence of bilateral invasive lobular carcinoma of the breast in different studies varies from 6 to 38% (2, 9). It is believed that patients with invasive lobular breast cancer have 25 to 50% greater risk of developing cancer in the other breast than the general population. As commonly pointed out, the possibility is higher if there is a positive family history (2). The patient presented in this report had a positive family history. A macroscopic tumour may present as a solid tumour mass with irregular edges or numerous

small nodes scattered in different quadrants (multi-centric tumours), and sometimes presents in the form of two or more nodes in the same breast quadrant (multifocal tumours) (12-14). Tumors can sometimes be large, and affect the entire breast, or they are of microscopic dimensions – clinically invisible. Multicentric tumours are seen in about 15 to 70% of breast cancer patients and more frequently in those with lobular than ductal carcinomas. It is believed that multicentric lobular carcinomas have a worse prognosis due to their higher potential to metastasize to the axillary lymph nodes (2, 12-14). An aggressive phenotype of multicentric lobular carcinoma was present in the case of our patient, whose primary tumour was discovered only after the appearance of metastases in the duodenum and colon. Breast cancers spread by local invasion, via lymph and blood circulation. Local tumour cells invade the parenchyma of the breast, nipple, fascia, pectoral muscles and other structures. Contrary to invasive ductal carcinoma which usually metastasizes to the liver, lungs and bones, invasive lobular carcinoma has affinity to metastasize to the peritoneum, retroperitoneum, and genitourinary system, where the metastases are usually present in the cervix, ovaries, and urinary bladder (15-20). On the basis of published autopsy series and rare case reports, it is estimated that the incidence of metastases of invasive lobular carcinoma of the breast in the gastrointestinal tract varies from 6% to 18% (21, 22). Based on autopsy studies, the reports indicate that in the gastrointestinal tract, the most common metastatic sites of lobular carcinoma are the stomach and small intestine (16, 23). In the diagnosis of distant metastases in the gastrointestinal tract, first of all, it is important to distinguish between the primary deposits and secondary neo-proliferation, and in order to confirm the diagnosis a biopsy of metastatic tumors is essential. In most cases, histopathological diagnosis may be difficult, especially since metastatic cells can often be less differentiated than those in the primary tumour. In such cases, immunohistochemical diagnosis is very valuable.

In its classic form, invasive lobular carcinoma is built of relatively small uniform cells that are individually arranged in narrow rows such as the Indian column ("Indian file" formation). Sometimes the tumour cells line up in concentric ("pagetoid") pattern around the duct lobule. Tumor stroma is usually abundant, dense, with the focus of periductal elastosis (2). It is estimated that about 80% of invasive lobular carcinoma contains the foci of lobular intraepithelial neoplasia (LIN) or lobular carcinoma "in situ" (LCIS) (24).

Immunohistochemically, tumor cells show a positive reaction to cytokeratin, EMA and membrane antigen of milk fat globules. The current therapeutic protocols require that for every breast cancer, immunohistochemical expression of estrogen (ER), progesterone receptors (PR), HER2 status, and Ki67 proliferative index are determined (25, 26). Using the histopathological analysis, we found both in the tumour tissue of each breasts and in the metastatic foci in the duodenum and colon in our patient the "Indian file" tissue arrangements, a very marked expression of estrogen receptors, pan-cytokeratin (AE1/AE3), Cytokeratina7 and EMA. It is known that, in contrast to ductal ones, lobular carcinomas do not have the expression of E-cadherin, which facilitates the diagnosis (25, 26). Some 35% of invasive lobular carcinomas show HER-2 expression. An excessive HER-2 manifestation is a good predictor of response to Herceptin, but it is not a good predictor of response to chemotherapy and survival of patients (2, 27).

Conclusion

In conclusion, we may point out that the case of our patient with bilateral multicentric breast cancer whose initial symptoms were gastrointestinal, speaks in favour of an aggressive and unpredictable phenotype of the tumor. It should be pointed out that distant breast cancer metastases in the GI tract often cause nonspecific symptoms and signs, which significantly delays the correct diagnosis and consequently worsens the prognosis.

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METASTAZE U DUODENUMU I KOLONU KAO PRVA MANIFESTACIJA MULTICENTRIČNOG, INVAZIVNOG LOBULARNOG KARCINOMA DOJKE

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Invazivni lobularni karcinom (ILC) je drugi po učestalosti maligni tumor dojke posle invazivnog dukalnog karcinoma. Incidencija bilateralnog ILC dojke varira od 6% do 38%, a najčešće metastazira u limfne noduse, kosti, pluća, pleuru, jetru, nadbubreg. Tumor ima afinitet da metastazira u peritoneum, retroperitoneum i genitourinarni sistem. S obzirom da ILC retko metastazira u gastrointestinalni trakt, u ovom izveštaju prikazujemo slučaj žene stare 58 godina sa bilateralnim, lobularnim, multicentričnim karcinomom dojke, koji se inicijalno prezentovao gastrointestinalnim simptomima zbog prisustva metastaza u duodenum i u kolon.

Na osnovu histološkog obrasca rasta i imunohistohemijskih karakteristika malignih ćelija u endoskopskim biopsijama duodenuma i kolona, nakon gastroduodenoskopije i kolonoskopije postavljena je sumnja na lobularni karcinom. Ultrazvukom i mamografijom je u obe dojke pronađeno više tumorskih čvorova malignih radioloških karakteristika, veličine do 7 mm, pa je urađena subkutana mastektomija sa disekcijom limfnih čvorova aksile sa desne strane i rekonstrukcija obe dojke sa ugradnjom silikonskih endoproteza. Konačna dijagnoza invazivnog bilateralnog multicentričnog karcinoma dojke postavljena je operativnim biopsijama.

Prikazan slučaj potvrđuje agresivni i nepredvidljivi fenotip ovog tumora, pri čemu treba imati na umu da prisustvo udaljenih metastaza u GIT-u obično izaziva nespecifične simptome i znake, što znatno doprinosi odloženoj dijagnozi i naknadno pogoršava prognozu bolesti. *Acta Medica Medianae 2016;55(4):60-65.*

Ključne reči: invazivni lobularni karcinom, udaljene metastaze, duodenum, kolon