

# An Increase of CA 19.9 as the First Clinical Sign of Ileocecal Valve Metastasis from Breast Cancer

DANIELE SANTINI<sup>1</sup>, ANNAMARIA ALTOMARE<sup>1</sup>, BRUNO VINCENZI<sup>1</sup>, GIUSEPPE PERRONE<sup>2</sup>, ANTONELLA BIANCHI<sup>2</sup>, CARLA RABITTI<sup>2</sup>, VINCENZO MONTESARCHIO<sup>4</sup>, VINCENZO ESPOSITO<sup>4,5</sup>, ALFONSO BALDI<sup>3</sup> and GIUSEPPE TONINI<sup>1</sup>

<sup>1</sup>Department of Medical Oncology and <sup>2</sup>Department of Pathology, University Campus Bio-Medico, Rome;

<sup>3</sup>Department of Biochemistry and Biophysics F. Cedrangolo, Section of Pathology, Second University of Naples, Naples;

<sup>4</sup>Third Division, D.Cotugno Hospital, Naples, Italy;

<sup>5</sup>International Society for the Study of Comparative Oncology, Silver Spring, MD, U.S.A.

**Abstract.** *Case Report: The case of a breast cancer patient with a progressive increase of CA 19.9 that indicated gastrointestinal metastasis is reported. After the observation of an increased CA 19.9 serum value (104.00; n.v. 0.0-37.00) a colonoscopy was performed. This examination showed the presence of an erythematous and granular zone near the ileocecal valve. Histological examination of biopsies taken during the colonoscopy revealed atypical monomorphic cells between the organoid pattern of the colon-type ducts. Immunohistochemical staining was positive for cytokeratin 7 and for estrogen receptors, consistent with metastatic epithelial malignancy. After eleven months, the patient presented with signs of intestinal obstruction, requiring an ileocolic bypass. At definitive histological examination, the tumor exhibited features of mammary metastases. Conclusion: This is the first report in the literature of an ileocecal valve metastasis from breast cancer diagnosed by an increase of CA 19.9, which is a marker of primary colorectal carcinoma.*

In western countries, breast cancer is the commonest female cancer in the fourth and fifth decades of life. During their lifetime, approximately 50% of the patients with breast cancer develop distant metastases: the most frequent locations are the lymph nodes, bone, lung and liver, while less common sites are the skin, brain and gastrointestinal tract (1). The most common histological subtype is invasive

ductal carcinoma, followed by lobular, medullary, tubular and mucinous carcinoma (2).

Lobular breast cancer has a specific metastatic pattern and, more frequently than ductal cancer, metastasizes to the gastrointestinal tract and the retroperitoneal tissue (3). The diagnosis of colorectal metastasis is difficult because of its non-specific clinical presentation and variable radiographic features. The real incidence of gastrointestinal metastases in breast cancer patients is probably underestimated because of the non-specific presentation symptoms and death of patients caused by other, more obvious, metastases (4).

The case of a breast cancer patient with a progressive increase of CA 19.9 (carbohydrate antigen), that indicated gastrointestinal metastasis, is reported.

## Case Report

In April 1998, a 73-year-old woman presented with an overclavicular lymphadenopathy; ultrasonography revealed a left side breast nodular lesion, which was confirmed mammographically. Histology of the lymph node biopsies implied metastatic breast cancer (lobular carcinoma histotype). Estrogen and progesterone receptors were determined by immunohistochemistry and resulted positive. For this reason, chemotherapy with Epirubicin and Vinorelbine was initiated. After six cycles, the patient underwent radiotherapy to the left breast nodule and the lymph node lesions.

The disease was stable until January 2001, when two lesions on the right and left hemithorax appeared and histological examination of the biopsies revealed a dermal infiltration, probably of mammarian origin. For this reason, chemotherapy was given, obtaining a disease stabilization.

In April 2002, the patient presented with multiple overclavicular, axillary and, later, cervical nodules. Because

*Correspondence to:* Daniele Santini, Oncology, University Campus Bio-Medico, Via Emilio Longoni, 69, 00155 Rome, Italy. Tel: 0039-06-22541737, Fax: 0039-06-22541520, e-mail: d.santini@unicampus.it

*Key Words:* Breast cancer, CA 19.9, ileocecal valve metastasis.

of this infiltration, a second line of chemotherapy was initiated. She showed stable disease until October 2002, when a CT scan confirmed a new disease progression. A cutaneous biopsy showed the presence of lobular carcinoma infiltration; a third line of chemotherapy with Paclitaxel was started. After the sixth cycle of this therapy, a CT scan showed stable disease.

In May 2003, a CA 19.9 evaluation was performed that showed an increased serum value (104.00; n.v. 0.0-37.00); with the suspicion of a primary colorectal cancer, a colonoscopy was performed. This examination showed the presence of an erythematous and granular zone near the ileocecal valve. Histological examination of the biopsies, taken during colonoscopy, revealed atypical monomorphic cells between the organoid pattern of the colon-type ducts (Figure 1). Immunohistochemical staining was positive for cytokeratin 7 (Figure 2A), though not for cytokeratin 20 (Figure 2B), and positive for estrogen receptors (Figure 2C), consistent with metastatic epithelial malignancy. Immunohistochemistry was negative for progesterone receptors (Figure 2D).

After eleven months, the patient presented with signs of intestinal obstruction; for this reason she was operated on and an ileocolic bypass was done. On histological examination the tumor exhibited features of mammary metastases.

In April 2004, because of disease progression, chemotherapy with Capecitabine was started. A CT scan after ten cycles of this therapy (January 2005) revealed a completely stable disease without peritoneal dissemination; the patient is continuing this treatment.

## Discussion

The metastatic spread of breast cancer to the lymph nodes, bone, lungs, liver and brain is well known; metastases involving the gastrointestinal tract are less common and less often recognized. In some cases, there is a long interval between diagnosis of primary breast cancer and the first clinical manifestation of gastrointestinal metastases (4-6). In other cases, gastrointestinal involvement is the first sign of breast cancer (7).

Secondary metastases due to the breast cancer are mainly found in the stomach and the colon and rectum (8, 9). The presenting symptoms and signs are non-specific and include nausea, vomiting, dysphagia, epigastric pain and melena if the stomach is the site of the tumor (8). Colorectal involvement may produce symptoms such as diarrhea, crampy pain, vomiting and palpable tumor (9). Small bowel metastases can also cause anemia, obstruction or perforation (10). In this case, the symptoms were absent and only an increase of the gastrointestinal marker CA 19.9 indicated intestinal

metastasis eleven months before the appearance of intestinal obstruction.

Usually CA 15.3 and CEA can be used in the routine monitoring of patients with breast cancer, even if neither of them are recommended for diagnosis, staging and routine surveillance because of the discordant results that have been observed (11). However, serum CA 19.9 elevation may be observed in as many as 20% to 40% of patients with late-stage colorectal cancer and progressive increases of the marker may signal disease progression, but not metastasis from another tumor (11). The diagnosis of gastrointestinal metastases is difficult. Radiography, with barium or water-soluble contrast material, conventional ultrasound and, especially, endoscopy with deep biopsy and echoendoscopy can help reach the final diagnosis (4, 8, 9).

Metastases of lobular carcinomas have a typical pattern of spread with intramural infiltration growing within the serosal, muscular and submucosal layers with small cells in "Indian files" cords throughout the tissue (4). Immunohistological staining can help to provide evidence of a metastatic epithelial malignancy, as in the presented case. However, an endoscopic biopsy may be negative in more than 50% of cases because the intramural lesion is inaccessible to the biopsy forceps (8).

In patients affected by breast cancer, abdominal pain and persistent gastric disorders must be investigated in an early attempt to document any possible gastrointestinal metastasis (4). Non-surgical treatment is applied when metastases in other sites are present or the condition of the patient is not favorable; in these cases, the overall response rate in breast cancer patients with gastric or colorectal metastases is, respectively, 32% and 53% (8, 9). Our patient was not operated on because she had no symptoms or signs of obstruction and she had lymph node metastases and dermal infiltration. Surgical treatment must be used in the case of isolated lesions and during emergencies (perforation or obstruction), which are the main cause of death among patients with known gastrointestinal metastases (8, 9). After diagnosis of gastrointestinal metastases, the median survival of patients is about one year (8, 9), even if the prognosis is fairly good when only a solitary metastasis is present (7). Important prognostic factors are other distant sites of metastases and local spread of the tumor (4).

In summary, this is the first report of an ileocecal valve metastasis from breast cancer that was diagnosed by an increase of CA 19.9, the marker of primary colorectal carcinoma. Gastrointestinal metastases are difficult to diagnose and this case suggests that every symptom or sign of gastrointestinal involvement in a breast cancer patient must be investigated so as not to delay the diagnosis of a metastatic tumor.

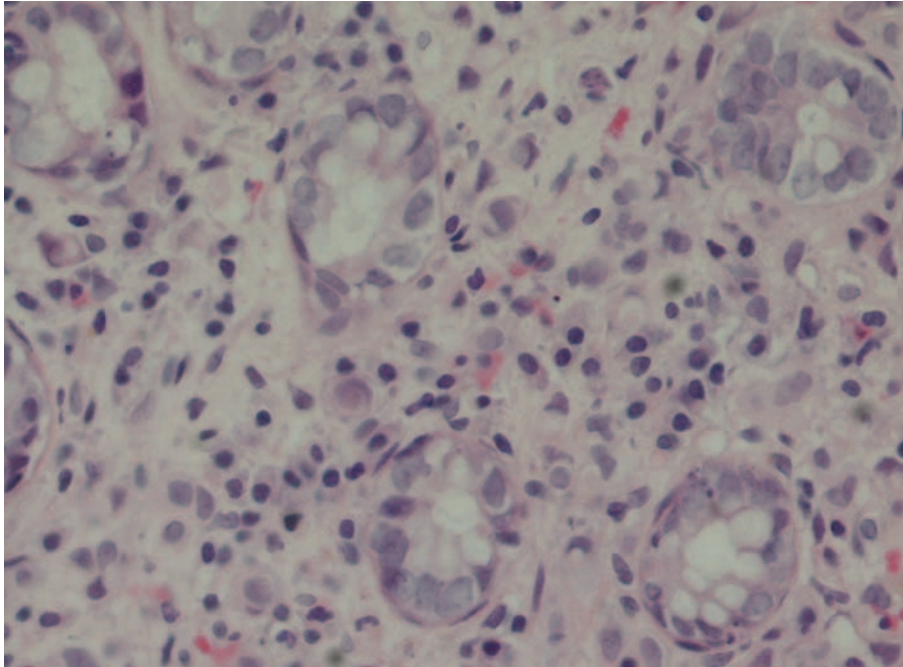


Figure 1. *Atypical monomorphic cells with nuclear alteration in the lamina propria of large bowel mucosa. (E.E., 400X)*

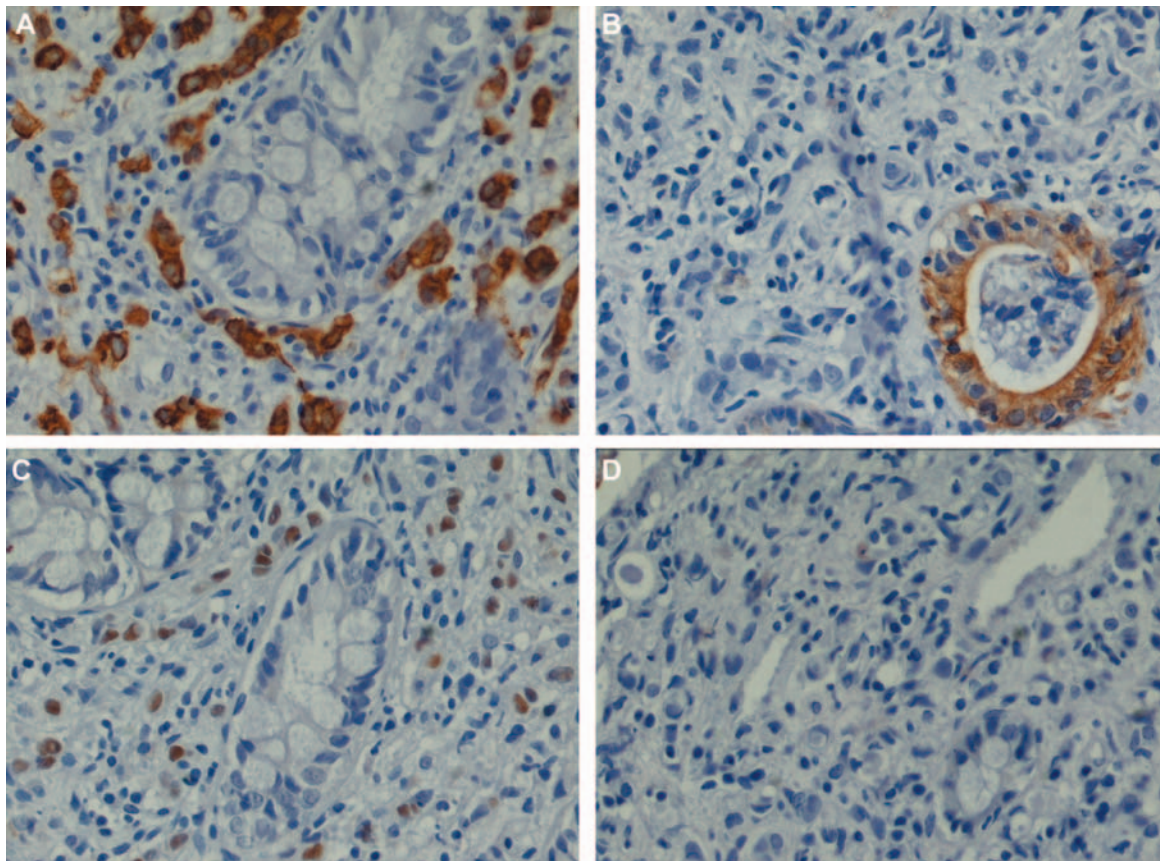


Figure 2. *Immunohistochemical staining: atypical monomorphic cells were positive for cytokeratin 7 (A) and negative for cytokeratin 20 (B); strong nuclear positivity for estrogen (C) and negative for progesterone receptors (D). (ABC, 400X)*



## Acknowledgements

This work was partially supported by a FUTURA-onlus grant to D.S., A.B. and G.T. We thank ISSCO (USA) for its continuous support.

## References

- 1 Cifuentes N and Pickren JW: Metastases from carcinoma of mammary gland: an autopsy study. *J Surg Oncol* 11: 193-205, 1979.
- 2 Harris M, Howell A, Chrissohou M *et al*: A comparison of the metastatic pattern of infiltrating lobular carcinoma and infiltrating duct carcinoma of the breast. *Br J Cancer* 50: 23-30, 1980.
- 3 Dixon AR, Ellis IO, Elston CW and Blamey RW: A comparison of the clinical metastatic patterns of invasive lobular and ductal carcinomas of the breast. *Br J Cancer* 63: 634-635, 1991.
- 4 Van Trappen Ph, Serreyn R, Elewaut AE *et al*: Abdominal pain with anorexia in patients with breast cancer. *Ann Oncol* 9: 1243-1245, 1998.
- 5 Stellakis MLC and Leach RD: Small bowel obstruction caused by a solitary metastasis from carcinoma of the breast. *Breast* 8: 139-140, 1999.
- 6 Kam MH, Barben CP, Eu KW and Seow-Choen F: Small bowel malignancies: a review of 29 patients at a single centre. *Colorectal Dis* 6: 195-197, 2004.
- 7 Ryden L, Chebil G and Jonsson Per-Ebbe: Small bowel obstruction caused by intestinal metastases from undiagnosed breast cancer: report of two cases. *Eur J Surg* 168: 648-650, 2002.
- 8 Taal BG, den Hartog Jager FCA, Steinmetz R *et al*: The spectrum of gastrointestinal metastases of breast carcinoma: I. Stomach. *Gastrointest Endoscopy* 38: 130-135, 1993.
- 9 Taal BG, den Hartog Jager FCA, Steinmetz R *et al*: The spectrum of gastrointestinal metastases of breast carcinoma: II. The colon and rectum. *Gastrointest Endoscopy* 38: 136-141, 1993.
- 10 Van Halteren HK, Peters H and Gerlag PGG: Large bowel mucosal metastases from breast cancer. *J Clin Oncol* 16: 3711-3713, 1998.
- 11 Bast RC *et al*: Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. *J Clin Oncol* 14: 2843-2877, 1996.

*Received July 15, 2005*

*Revised October 17, 2005*

*Accepted October 20, 2005*