

Research Article

Colorectal Metastasis Secondary to Breast Cancer

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Abstract

Even though colorectal metastasis from a primary breast cancer is rare, it is important for primary care providers who follow cured breast cancer patients and colorectal surgeons who encounter patients with history of breast cancer presenting with gastrointestinal symptoms, to keep in mind that colorectal metastasis from a primary breast cancer should be included in the differential diagnosis for any woman with a previous history of breast cancer presenting with a new gastrointestinal complaint.

Keywords: Breast cancer; Colorectal metastasis; Gastrointestinal symptoms

Introduction

Over the last decade tremendous advancement in the current therapeutic regimens implicated in the treatment of breast cancer have been achieved. This advancement has significantly decreased the mortality rates and increased the overall survival rates for patients diagnosed with breast cancer. Hence, more patients with history of breast cancer presenting with metastatic disease will be encountered in the clinical practice. In fact, approximately 25% of all metastases from breast cancer occur beyond the first 5 years of the diagnosis of early-stage disease [1]. Breast cancer typically metastasizes to the lungs, bones, liver, adrenal and brain and in rare instances can metastasize to the gastrointestinal tract. Having said this and in view of the increased survival rate in patients with breast cancer, more patients with history of breast cancer presenting with unusual presentations will be encountered in the clinical practice. Among these unusual presentations is the gastrointestinal tract metastasis and specifically metastasis to the colon and rectum. From here, colorectal metastasis secondary to breast cancer should be included in the differential diagnosis of any woman with a previous history of breast cancer presenting with a new gastrointestinal complaint. Herein, we present a review of literature regarding colorectal metastasis from a primary breast cancer, focusing on the clinical presentation, pathology of the primary breast cancer, diagnostic workup, and options for management.

Materials and Methods

In this review, we examined the reported cases and reported case series of breast cancer metastasizing to the colon and rectum to

identify points that could help primary care physicians and colorectal surgeons in diagnoses and management of such a rare entity. We electronically searched PubMed, Medline, Embase, Cancerlit and Google Scholar databases for articles published between 1950 and 2020 using the following keywords: “colorectal metastasis”, “breast cancer”, “metastatic breast cancer”, “breast cancer distant metastasis”. All case reports and case series were thoroughly examined, and data regarding pathology of the primary breast cancer, mechanism of spread, signs and symptoms, diagnostic workup, and management were systematically reviewed.

Background

Secondary tumors of the colon and rectum are rare and its incidence is not well documented, presenting a challenge to the unaware. These secondary tumors develop by means of direct extension of a nearby organ, peritoneal seeding or hematologic spread. With peritoneal seeding being the most common mode of invasion, hence it is much more common to see secondary colonic tumor due to ovarian cancer invasion rather than those related to hematogeneous spread from breast cancer. However, over the last decade, there has been a dramatic increase in the survival rates of breast cancer patients due to improvement in breast cancer management owed to better screening modalities, timely diagnosis and better treatment options on the level of hormonal therapy, adjuvant chemotherapy and radiotherapy. Despite this, metastasis from breast cancer still occurs in up to 30 percent of patients despite treatment by chemotherapy, radiotherapy and hormonal therapy [2]. Having said this, it is expected that more patients with history of breast cancer presenting with metastatic disease will be encountered in the clinical practice. Breast cancer typically metastasizes to the lungs, bones, liver, adrenal and brain and in rare instances can metastasize to the gastrointestinal tract. Metastasis to the gastrointestinal tract is rare and involvement can occur anywhere from the oropharynx to the anus [3]. Colon and rectal metastasis from breast cancer is extremely rare, reported in the medical literature as case reports and few case series, with no reviews. To the best of our knowledge, 109 cases of colorectal metastasis have been reported in the medical literature, these are divided into 93 colonic metastasis and 16 rectal metastasis (Table 1).

Taal et al. [4] reported 17 cases of colorectal metastasis from

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Table 1: Published literature on colorectal metastasis from breast cancer.

Author	Number of patients	Primary breast histology	Estrogen/ progesterone receptors	Age at presentation of colorectal metastasis	Time from diagnosis	Distant site	Treatment	Notes
Taal et al. [4]	17	15 lobular 1 ductal 1 not known	Not Known	60 years (42-76)	53 months	Colon and Rectum	3 Resection + Systemic therapy 2 Radiotherapy 12 Systemic	
Schwarz et al. [5]	1	Lobular/ ductal	Not Known	78 years	3 months	Colon	Resection	
Wiisanen et al. [6]	6	2 Lobular 1 Ductal 3 unknown	Not Known	Not Known	Not Known	Colon	Not Known	
Borst and Ingold [9]	3	3 lobular	Not known	Not known	Not known	Colon	Not known	
Winston et al. [22]	15	15 lobular	Not known	Not known	Not known	Colon	Not known	
Uskent et al. [23]	2	1 lobular 1 lobular	Positive/ positive Positive/ positive	41 years 43 years	108 months 37 months	Colon Colon	Palliation Systemic chemotherapy Resection and systemic therapy	Synchronous with stomach
Koutsomanis et al.	1	Ductal	Not Known	65 years	48 months	Colon	Resection and systemic therapy	
Yokota et al. [25]	1	Ductal	Not Known	57 years	120 months	Colon	Resection	
Vaidya et al. [24]	1	Ductal	Not Known	56 years	60 months	Colon	Resection and systemic therapy	
Rabau et al. [26]	1	Lobular	Not Known	53 years	84 months	Colon	Resection	
Gifaldi et al. [10]	1	Lobular	Not Known	86 years	120 months	Colon	Resection and systemic therapy	
Voravud et al. [27]	1	Lobular	Not Known	74 years	6 months	Colon	Resection	
Uygun et al. [28]	1	Ductal/ Lobular	Negative/ positive	38 years	60 months	Colon	Resection and systemic therapy	
Zhang et al. [29]	2	1 Lobular 1 Lobular	Positive/ not known Positive/ not known	64 years 59 years	Not known Not known	Colon Colon	Not known Not known	
Nazareno et al. [30]	1	Not known	Not known	52 years	60 months	Colon	Not known	3 lesions in the colon
Falco et al. [31]	1	Lobular	Positive/ Positive	67 years	120 months	Colon	Resection	
Zhou et al. [32]	1	Ductal	Positive/ positive	54 years	108 months	Colon	Systemic therapy	
Sharbatji et al. [33]	1	Lobular	Positive/ positive	72 years	120 months	Colon	Resection	
Nejati et al. [34]	1	Ductal	Positive/ positive	37 years	48 months	Colon	Palliative	
Critchley et al. [35]	1	Lobular	Positive/ not known	62 years	96 months	Colon	Systemic therapy	Synchronous to the stomach
Okida et al. [36]	1	Lobular/ ductal	Negative/ positive	48 years	60 months	Colon	Resection	
Theraux et al. [37]	1	Lobular	Not known/ Not known	63 years	60 months	Colon	Hartman	
Dhar et al. [38]	1	Intraductal papillary	Not known	75 years	72 months	Colon	Resection	
Shimonov et al. [39]	2	1 Ductal 1 Ductal	Not known Not known	65 years 73 years	24 months 72 months	Colon Colon	Resection and systemic therapy Resection	
Vaidya et al. [24]	1	Ductal	Not known	56 years	60 months	Colon	Not known	
Signorelli et al. [40]	1	Lobular	Not known	62 years	144 months	Colon	Resection and systemic therapy	
Murukutla et al. [41]	1	Ductal	Positive/ positive	59 years	12 months	Colon	Systemic therapy	
Feng et al. [42]	1	Ductal	Not known	49 years	24 months	Colon	Not known	
Alves de Lima et al. [43]	1	Lobular	Not known	74 year	84 months	Colon	Chemotherapy and resection	
Ee Ng et al. [44]	1	Lobular/ ductal	Positive/ positive	56 years	60 months	Rectum	Systemic therapy	Positive fecal occult blood
McLemore et al. [7]	1	Ductal	Not known	Not known	Not known	Rectum	Systemic therapy	
Cervi et al.	1	Lobular	Not known	59 years	96 months	Rectum	Not known	
Wiisanen et al. [6]	2	1 Lobular 1 Ductal	Not Known	Not Known	Not Known	Rectum	Not Known	
Asch et al.	3	Not known Not known Not known	Not known	58 years 75 years Not known	78 months 18 months Not known	Rectum Rectum Rectum	Colostomy Colostomy Not known	
Klein and Sherlock	2	1 Lobular 1 Not known	Not known	68 years 77 years	56 months 276 months	Rectum Rectum	Radiotherapy Radiotherapy	
Haubrich et al.	1	Ductal	Not known	56 years	36 months	Rectum	Supportive	
Bamias et al.	1	Lobular	Positive/ positive	74 years	108 months	Rectum	Resection and chemotherapy	
Arrangoiz et al.	1	Lobular	Positive/ positive	70 years	0 months	Rectum	Chemotherapy	

Rajan et al.	1	Ductal	Positive/ not known	60 years	108 months	Rectum	Radiotherapy Resection
Shimonov et al.	1	Lobular	Not known	72 years	144 months	Rectum	Resection
Efthimiadis et al.	1	Lobular	Not known	74 years	60 months	Rectum	Resection and radiotherapy

breast cancer over a 15-year period. The primary tumor was lobular carcinoma in 15 patients (15/17, 88 percent), patients presented with colorectal metastasis on an average of 53 months after the initial treatment for their breast cancer and their average survival time was 16 months.

Schwarz et al. [5] reported 7 cases of breast cancer metastasis to the gastrointestinal tract, among which only one out of 7 patients had colonic metastasis. Patient presented with gastrointestinal symptoms 3 months after the diagnosis of breast cancer. The histology of breast cancer showed a mixed lobular and ductal carcinoma. Colonic metastasis was treated surgically by resection and patient was disease free after 19 months of follow up.

Furthermore, Mayo Clinic reported 32 cases of breast cancers metastasizing to the gastrointestinal tract and peritoneum [6]. 6 colonic and 2 rectal metastasis were identified, with lobular carcinoma being the most common histology in all gastrointestinal metastasis. The time from original breast cancer diagnosis to gastrointestinal metastases was 6.7 years.

On the other hand, McLemore et al. [7] reported 73 cases of breast cancer with gastrointestinal or peritoneal metastasis after a retrospective review of all patients with breast cancer between 1985 and 2000. Out of these 73 patients, 23 had GI metastasis only, 32 had carcinomatosis only, and 18 were diagnosed with both. The gastrointestinal metastasis rate was most commonly to the colon and rectum with 45% of the patients, contrary to the previous reported series. 24 patients with colorectal metastasis among which 23 patients had colonic metastasis and 1 rectal metastasis.

Impact of the histology of breast cancer

The tendency of metastasis to the gastrointestinal tract from breast cancer may be related to the histologic subtype of breast cancer. The major histologic subtypes of breast cancer are ductal carcinoma and lobular carcinoma, with ductal carcinoma accounting for 90% of cases [8] and lobular carcinoma accounting for 8% to 14% of cases [9]. Even though it's rarer, the lobular form of breast cancer is more likely to metastasize to the colon [10,9]. In fact, Borst and Ingold reported a series of 2,600 cases of breast cancer with metastasis to the gastrointestinal tract. Among which, 359 cases of lobular carcinoma was identified and 2,246 cases of ductal carcinoma identified. Of these cases, 4.5% in the lobular vs. 0.2% in ductal carcinoma group developed gastrointestinal tract metastasis. They concluded that lobular carcinoma tends to metastasize more to the GI tract in contrast to ductal carcinoma [9].

In fact reviewing all the reported cases and case series (Table 1) showed that for colonic metastasis secondary to breast cancer the most common type of primary breast cancer was lobular carcinoma in 66 percent of cases followed by ductal carcinoma in 20 percent of cases and 4 percent for mixed types. On the other hand, regarding the rectal metastasis 44 percent were lobular carcinoma and 25 percent ductal carcinoma.

From the breast to the colon and rectum: Mechanism of spread

The exact mechanism behind this unusual metastatic pattern is controversial. The loss of E cadherin expression on tumor cell membrane is a characteristic feature of lobular carcinoma. E cadherins are epithelial specific, cell to cell adhesion molecules that are responsible for the maintenance of differentiation and prevention of cellular invasion. In normal glands, these molecules are well expressed at the borders of epithelial cells and the loss of these molecules as a result of the inactivation of the CDH1 gene at 16q22 has been implicated in lobular breast carcinomas. The loss of E cadherin expression is associated with abnormalities in catenin expression, leading to the loss of cell to cell adhesion and facilitates tumor cell migration, as well as intra and intercellular signaling. In addition, the loss of CDH1 expression is also believed to confer the highly discohesive morphology characteristic of this tumor subtype, and is often associated with tumor invasion and metastasis, which rarely occurs in other tumor types [11,12]. Furthermore, it is common for oncologic patients to be on steroid and it is known that patients receiving steroids may develop metastasis at unusual sites due to the possible influence of the immunosuppressive effect of steroids [13].

Clinical Presentation

As evident from the 109 cases reviewed (Table 1) the mean age of presentation is 60 years for colonic metastasis and 67 years for rectal metastasis. Furthermore, the mean time from the primary diagnosis till the presentation is 69 months for colonic metastasis and 87 months for rectal metastasis.

The clinical presentation of colorectal metastasis secondary to breast cancer is nonspecific and can mimic primary tumors of the colon and rectum or Crohn's disease, both clinically and radiologically [4,10,14]. Having said this, patients presents with a wide spectrum of complaints with symptoms ranging from abdominal pain, bloating, melena, bleeding, obstruction, nausea and vomiting, weight loss, anemia or fatigue, palpable mass till reaching the emergency presentation with bowel perforation and large bowel obstruction.

Workup

The diagnosis of gastrointestinal metastasis secondary to breast cancer can be difficult and is considered a challenge to the unaware for several reasons. First, the delayed presentation, sometimes years after the primary diagnosis, second the wide range of presenting symptoms which are seen in more common pathologies, third the challenge faced by the pathologist for its diagnosis and finally its rarity as a clinical entity.

Furthermore, what adds to the difficulty in the diagnosis is that endoscopic biopsy provide a moderate diagnostic yield and findings are normal in up to 50% of patients, perhaps because tumor growth is likely to be sub mucosal and focal. Having said this, endoscopic biopsies from metastatic ductal carcinoma are more likely to be positive (90%) than those from lobular carcinoma (64%) [15]. This is probably related to the metastatic pattern of lobular carcinoma that differs from ductal carcinoma in that it tends to occur as a diffuse thickening of mucosa rather than a discrete nodule and has a higher propensity to metastasize to serosal surfaces such as the gastrointestinal tract [16,17].

Aforementioned, the radiologic findings for colorectal metastasis secondary to breast cancer is wide as well, whereby diffuse versus multifocal involvement can be detected on CT scan or air contrast barium enema. Furthermore, stenosis, mucosal nodularity, decreased distensibility, and solitary apple core lesions can be detected [4,14].

Controversies in management

The management of colorectal metastasis secondary to breast cancer is debatable and multifactorial. Factors influencing the management approach depend on the presentation of the patient, being it an emergency presentation or a chronic one, the preoperative diagnosis, that is, is the tumor diagnosed as primary colorectal tumor *versus* colorectal breast metastasis. Finally, the degree of dissemination of the disease being it isolated metastasis to the colon and rectum, or a diffuse multi organ metastasis. Having said this, and because of the improved survival in patients with breast cancer giving time for colorectal metastasis secondary to breast cancer to appear more the question on the rise will be: When to operate for colorectal metastasis secondary to breast cancer?

Currently there is no consensus on the optimal management approach for colorectal metastasis secondary to breast cancer being it hormonal therapy or chemotherapy or radiotherapy with or without surgery. Some reports focusing on management of colorectal metastasis secondary to breast cancer suggested that patients can survive for long periods after the diagnosis and treatment of colonic metastases. Hence, an increased awareness and earlier aggressive approach may improve the prognosis [18]. Furthermore, systemic hormonal therapy, chemotherapy, or radiation therapy, either alone or as a complementary to surgery, has produced a favorable response in more than half of patients concerned, thus avoiding surgical intervention [4], except in emergency situations such as obstruction, bleeding, or perforation. On the contrary, Mourra et al. [19] reported that no individual with metastatic colon cancer regardless of the organ of origin has survived beyond 5 years. Hence, improving the patients' quality of life should be the aim, because achieving a complete remission at this stage of the disease is almost impossible, at least for the current date. Furthermore, given the rarity of colorectal metastasis secondary to breast cancer makes a randomized prospective trial comparing surgery versus medical approaches highly unlikely. Hence, tailored approach with careful patient selection being urgent versus non urgent, isolated versus non isolated remains the best approach.

Histologic approach

As for when the pathologist is concerned, immunohistochemistry is essential in reaching the diagnosis. The most essential markers to differentiate between primary colorectal malignancy versus metastatic breast cancer are gross cystic disease fluid protein-15 (GCDFP-15), estrogen and progesterone receptors. Metastatic breast carcinomas are usually positive for GCDFP-15 and often for estrogen and progesterone receptors in contrast to most colorectal carcinomas, which are negative [20,21].

Conclusion

Diagnosis of colorectal metastasis secondary to breast cancer is a rare entity, usually encountered years after the diagnosis of breast cancer. Its diagnosis is a challenge to the unaware and requires a high index of clinical suspicion for its diagnosis. These patients are more likely to present to a primary care provider, gastroenterologist, or colorectal surgeon than a breast surgeon. Therefore a high index of

clinical suspicion with early colonoscopy in those with non-specific symptoms and a past history of breast cancer, particularly lobular carcinoma, are recommended. It should be among the differential diagnosis of any woman with history of breast cancer presenting with new onset of gastrointestinal complaints. Currently, a tailored approach with careful patient selection being urgent *versus* non urgent, isolated versus non isolated remains the best approach in managing these patients.

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