

Destination Unknown: A Unique Case of Metastatic Colorectal Carcinoma to the Breast, Axilla & Skin

Shariful Islam^{1,2*}, Aneela Shah^{1,2}, Avidesh Mahabir¹, Sarah Dial^{1,2} and Vijay Naraynsingh²

¹San Fernando General Hospital (SFGH, SWRHA), San Fernando, Trinidad

²Department of Clinical Surgical Science, UWI, St Augustine, T&T

*Corresponding author: Shariful Islam, MBBS, DM (Surgery), FACS, FASBrS, Consultant General, Laparoscopic and Oncoplastic Breast Surgery, San Fernando Teaching Hospital Associate Lecturer, Department of Clinical Surgical Sciences, University of the West Indies, St Augustine, Trinidad and Tobago



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ABSTRACT

The commonest sites of distal colorectal cancer spread are the liver and the lungs. Metastasis to the skin, breast and axilla are very rare. Very little data exists regarding the optimal treatment methods and its long-term outcomes. We present a unique case of colorectal cancer patient who initially presented with solitary hepatic metastasis, subsequently underwent low anterior resection with synchronous resection of the hepatic mets after neoadjuvant chemotherapy. At one year followup, she developed a cutaneous, mets to right lateral chest wall and treated with wide local excision and adjuvant therapy. At four years of follow up she again develops metastasis to the right breast and axillary lymph node. Wide local excision of the breast lump and axillary lymph node dissection were performed. Despite recurrent metastasis the patient has maintained a good functional status. A literature review was done to highlight the best treatment options in these rare cases.

Keywords: Colorectal Cancer; Rare Site Metastasis; Mets To Breast; Axilla and Skin

Introduction

Hellman and Weichsel Baum first proposed the theory of oligometastasis in 1995. This concept recognizes that in some cancer patients, a limited number of metastases may suggest improved patient outcomes with local removal [1]. Thus, the traditional view of metastatic disease has changed, with treatment now aimed at cure, instead of prolonged survival or palliative care in some cases of metastatic disease. Perhaps the most common malignancy to undergo such a significant alteration in treatment is that of colorectal cancer. Metastases to the liver and lung can now be considered amenable to local resection or ablative therapies. Colorectal carcinoma is globally the third most common malignancy diagnosed each year. In the united states, 15-20% of patients have metastatic disease at the time of diagnosis. Modern systemic therapies have helped to improve the survival for such patients with nearly 20% surviving up to five years beyond diagnosis [2]. Published data has demonstrated that surgery can provide a cure in cases of isolated metastases and, when combined with systemic

therapies, can also improve long-term survival in cases where metastases involve more than organs [3]. However, much of this data is centered around metastases involving the liver and lung, as these are the commonest sites of distant colorectal cancer spread. Metastasis to the skin, breast and axilla, however, are far rarer and there is very little data regarding the optimal treatment strategy and long-term outcomes, even in cases of isolated lesions. The case presented here describes the clinical history of a lady diagnosed with primary colorectal carcinoma with a solitary hepatic metastasis. One year after undergoing intended curative treatment, she developed cutaneous, right breast and axillary metastases, each of which were treated with aggressive local resection. Despite this, she has maintained a good functional status with isolated recurrences at four years from her initial diagnosis. The discussion is based on the approach to best treatment in such rare cases: whether aggressive surgical resection should be sought in favour of limiting options to systemic palliative therapy alone.

The Case

A 55-year-old female, presented to the outpatient breast clinic for evaluation of right sided breast and axillary lumps which she noticed nine months prior and were increasing in size. She reported no breast pain, skin or nipple/areolar complex changes or nipple discharge over this period. She experienced menarche at 14 years old and was nulliparous, still experiencing regular menstrual cycles. She had never used oral contraception or hormone replacement and had no significant family history of breast or other malignancies. The patient had a complex past medical history, which included hypothyroidism treated with levothyroxine and Hodgkin's lymphoma treated with chest wall radiation 25 years ago. At that time, complications of treatment for her lymphoma included a frozen right shoulder as well as a right upper limb deep vein thrombosis. More recently (4 years prior to this presentation), she was diagnosed with an adenocarcinoma of the rectosigmoid colon with a solitary hepatic metastasis at segment 6. She underwent neoadjuvant chemoradiation followed by a low anterior resection and synchronous resection of her liver metastasis. She completed adjuvant chemotherapy but subsequently developed a solitary metastatic skin lesion at the site of her previous liver marker placement at the right lateral abdominal wall. This was treated with wide local excision and further systemic chemotherapy. Surveillance colonoscopy and computed tomography imaging showed no evidence of disease recurrence up to the time of presentation. The patient was a non-smoker and was functionally independent, but had limited right shoulder mobility.

At examination, the patient's vital signs were within normal limits with no signs of dehydration, anaemia, malnutrition or jaundice. Abdominal and rectal examinations showed no

abnormalities. Breast and axillary examinations revealed a 3 cm firm, mobile mass in the axillary tail of the right breast with an associated 2 cm firm palpable right axillary lymph node (Figure 1). Complete blood count, renal, liver and thyroid function tests were within normal limits. Ultrasound imaging confirmed the presence of a 2.2 cm solid, heterogenous mass at the upper outer aspect of the right breast, along with a 2 cm right axillary lymph node. Mammogram reported the presence of two enlarged, hyper dense right axillary lymph nodes, classed as BIRADS 5 lesions (Figure 2). CT confirmed the presence of a 2.6 cm spiculated lesion in the right upper outer breast with associated level I axillary lymphadenopathy (Figure 3). No other metastatic lesions were identified on CT. Positron Emission Tomography (PET) scan was not accessible to assess for other possible metastases. Core needle biopsy confirmed the presence of a metastatic colon adenocarcinoma within the breast and axillary lymph nodes, with tumour cells staining positive for cytokeratin CK20 (Figure 4). A joint decision with the patient was made to perform a wide local excision with axillary lymph node dissection. Under general anaesthesia, the patient was placed supine with the right shoulder abducted to ninety degrees. A cutaneous nodular lesion on the axillary skin was noticed at the time of surgery and this was excised under suspicion of a possible cutaneous metastasis (Figure 5). Through the same incision, a wide local excision of the breast lesion was performed with gross margins at least 1-2 cm and axillary lymph node dissection was completed to include levels I and II nodes. The thoracodorsal and long thoracic nerves were identified and preserved. A drain was inserted and the wound was closed in two layers. The patient had an uneventful recovery with no significant change in her shoulder mobility immediately after surgery. She was discharged home on post-operative day one with subsequent follow up at the clinic.



Figure 1: Image showing right axillary tail mass and associated axillary lymphadenopathy (encircled).

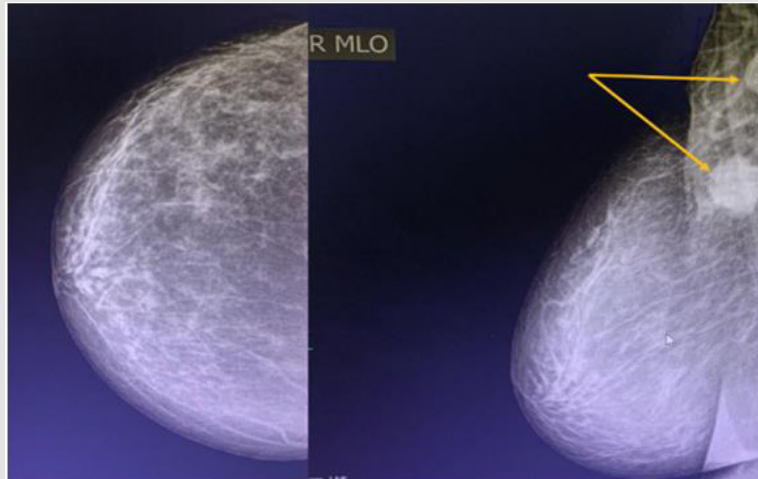


Figure 2: Craniocaudal (left) and mediolateral oblique (right) mammogram images demonstrating suspicious, enlarged right axillary lymph nodes (yellow arrows).

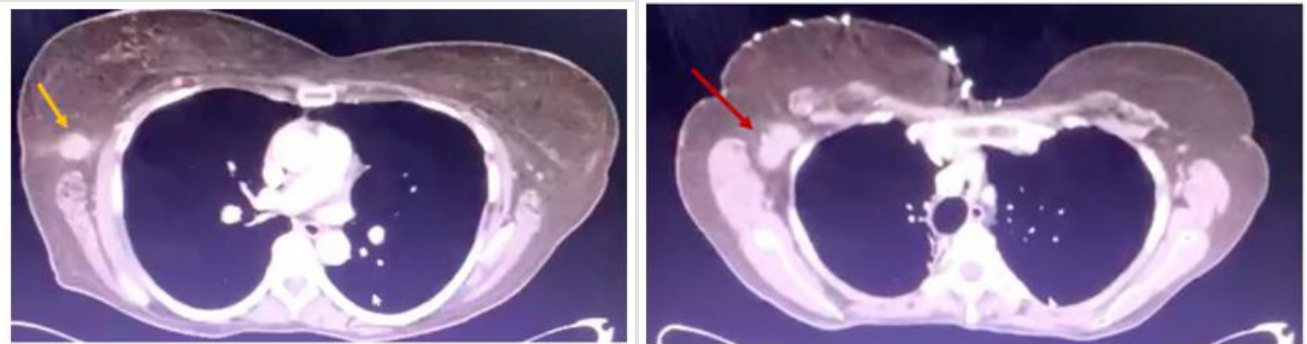


Figure 3: Axial CT images identifying a suspicious lesion within the axillary tail of the right breast (yellow arrow) and a suspicious, enlarged right axillary lymph node (red arrow).

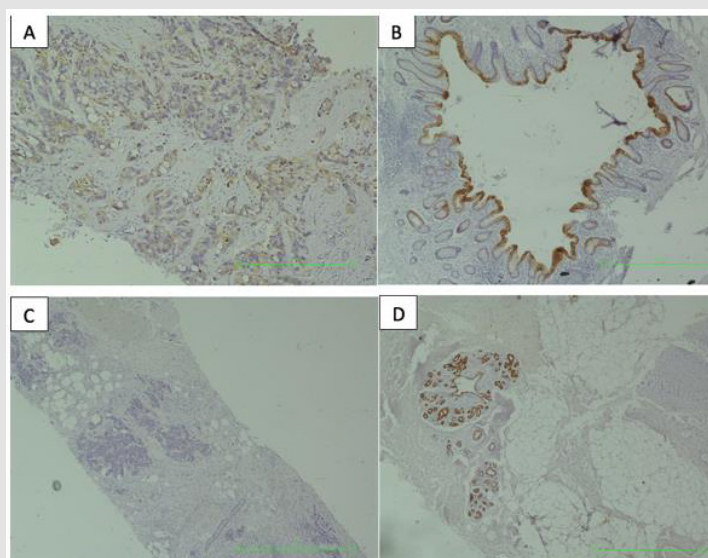


Figure 4: Microscopic appearance of the patient’s breast biopsy, staining positive for CK20 (A) with control (B) and negative for CK7 (C) with control (D).



Figure 5: Pre-operative image showing right breast lesion (yellow arrow), cutaneous nodule (red arrow) and site of excision of previous abdominal cutaneous metastasis (white arrow).

Discussion

Colorectal carcinoma is the third most common malignancy diagnosed around the world with a lifetime risk in developed countries as high as 4% [2]. In the Caribbean, this disease ranks among the top five leading cancers diagnosed annually in both males and females. Warner et al reported incidence rates of almost 11% and 3% for colon and rectal cancers respectively in Trinidad and Tobago between 1995 and 2009. They also reported that over 10% of most cancers in Trinidad and Tobago (including colorectal) were diagnosed at advanced stages, which highlights that tumour biology in this region may be particularly aggressive or that cancers are not diagnosed early enough [4]. Cancer metastasis is a complex multi-step process by which cancer cells acquire certain properties that allow them to move from the primary tumour and invade a distant organ. They do this while maintaining the ability to survive and travel within the body (directly entering the bloodstream or indirectly via lymphatic's) . Some circulating tumour cells are postulated to remain dormant while maintaining the ability to grow and this is thought to be one of the contributing factors responsible for the development of metastases after a primary tumour is removed [5]. The patient in the case presented here developed rare distant metastases three years after undergoing treatment with curative intent for colorectal carcinoma with a solitary hepatic metastasis. Unlike skin metastases occurring in 24% of metastatic breast carcinomas, data suggests that cutaneous metastases occur in just 4% (2.3-6%) of colorectal carcinomas. They are mostly found on the skin of the abdominal wall, especially at the sites of surgical scars related to treatment of the primary tumour, as occurred in this case [6].

Kauffman and Sina suggested that the pathogenesis of cutaneous metastases in colorectal cancer occurs due to lymphatic or haematogenous spread, spread along embryonic ligaments or, as postulated in this case, by direct seeding of tumour cells during a

surgical procedure. Published data suggests cutaneous spread tends to be identified within two years of undergoing cancer treatment. It is usually thought to signify widely disseminated disease and generally a poorer prognosis, with patient survival documented to be an average of 18 months (1-34 months) [7]. Based on a small number of case reports of this entity, recommendations suggest that single cutaneous metastases should undergo wide excision with margins at least 1 cm, as was performed in this case. This is in contrast to cases of diffuse cutaneous metastases which are generally treated by palliative systemic therapies [8]. Despite statistics suggesting relatively poor survival outcomes, this patient has now survived up to four years since her initial diagnosis. Although she has developed rare distant organ metastases, they continue to be isolated to single organs only. This has contributed to the decision to continue local excisions in combination with systemic therapy with the intention to improve her survival. Furthermore, the question of whether this approach to her treatment may actually provide a cure is yet unknown. Perhaps cure may not be possible in her case, as she has continued to develop distant metastases despite being on systemic chemotherapy. PET/CT, in our opinion, would have been beneficial in identifying occult metastases not detected by CT and may have helped to determine whether this patient was a candidate for surgery or not. The use of PET scanning is currently recommended by the National Comprehensive Cancer Network (NCCN) guidelines in patients who appear to have potentially resectable or curable metastatic colorectal carcinoma [9].

The most common primary tumours associated with breast metastases include cancers of the contralateral breast, leukaemia, melanoma, lung, ovary and stomach [10]. Distant metastasis of colorectal carcinoma to the breast, however, is extremely rare, with a handful of cases reported in the literature. Even rarer, is the involvement of axillary lymph nodes as described by Perin et al [11]. An analysis of 32 cases of this entity by Zhang et al found that the majority (94%) occur in females at an average age of 51

years and at a time ranging from 1 to 10 years after initial diagnosis of the primary tumour [12]. In the case presented here, for cancer cells to reach the breast and axilla having had previous involvement of the liver and skin, suggests that this patient's disseminated disease is particularly aggressive, with travel specifically along the haematogenous and lymphatic's. Imaizumi et al described possible lymphatic spread via the thoracic duct or superficial lymphatic's. However, Kawamura et al demonstrated that the superficial system may be more pertinent in the evolution of axillary lymph node involvement as the abdominal wall superior to the umbilicus drains upwards into the axillary nodes [13]. Unlike published reports of involvement of the left breast in 55% of cases, this patient's metastatic lesion occurred on the right breast, but similar to documented cases, her breast lesion was superficial, located in the upper outer quadrant, was mobile and fell within the reported size range (between 1 and 10 cm) [3] [12]. Shah et al described certain clinical or radiological features that may distinguish metastatic colorectal carcinoma of the breast from primary breast carcinoma: location within the subcutaneous fat and not the breast gland, rapid increase in size and lack of micro calcifications on breast imaging. Features like nipple retraction and skin tethering that are commonly seen in primary breast carcinoma are virtually non-existent in metastases to the breast. Such distant metastases of colorectal origin typically show mucinous or signet-ring features with the presence of lymphovascular invasion and a lack of elastosis or an in-situ component [14].

Immuno-histochemical analysis confirms the final diagnosis: cells at these sites stain positive for colorectal markers including cytokeratin 20 (CK20) and carcinoembryonic antigen (CEA) and are negative for markers of breast origin (CK7, oestrogen/progesterone receptor) [3]. The documented prognosis in cases of metastatic colorectal carcinoma to the breast is generally poor, with average survival rates less than 12 months from the time of diagnosis [3] [12]. However, individual case reports suggest that some patients may potentially achieve long-term survival. A case report by Imaizumi et al documented a nine-year survival between the time of initial diagnosis of colon cancer and axillary lymph node recurrence, suggesting that tumour biology may influence the metastatic potential in such cases [13]. Traditionally, the treatment of metastatic disease is based on the pathogenesis and biology of the primary tumour. From as early as 1894 Halstead proposed that breast cancer spread via a contiguous pattern along lymph nodes from the primary tumour ultimately to distant sites. More recently, the systemic theory suggested cancer is a systemic disease process: meaning that if a tumour is going to metastasise, it has already done so. This theory remarks that cancer spread does not occur in a contiguous fashion as Halstead proposed, but rather clinically apparent lymph nodes are manifestations of already distant metastasis. However, both these theories are limited in their ability to fully describe cancer behaviour.

The systemic theory does not account for the existence of intermediate disease states between localized and metastatic and while the contiguous theory may cover this, it does not account for the ability of cancer to spread through the bloodstream. Intensive study of tumour biology since then has led to the understanding of cancer behaviour, which lies on a spectrum ranging from localized to distant metastatic disease. During the evolution of invasive malignancy, tumour cells are now understood to acquire several features which enable metastatic spread to occur in a multistep fashion. This knowledge formulated the basis for Hellman's and Weichselbaum's concept of oligometastases, which proposes that the biology of a tumour predicts if its metastatic potential is limited to specific regions. Tumour size and pathological grade are perhaps the two most frequently used characteristics that may help guide knowledge on a cancer's oligometastatic potential. On the contrary, this is vastly different from the term micro metastases, which describes very small but extensive cancer metastases. Colorectal carcinoma is one of the most commonly described malignancies that can exist in an oligometastatic state. Successful treatment with good survival outcomes is well documented, particularly in the treatment of hepatic or pulmonary metastases [1].

An oligometastatic state theoretically puts forward the possibility that malignant disease can be amenable to cure, with therapies targeted towards treating both the primary tumour and the limited extent of metastatic lesions. But, for treatment to be effective, all metastatic sites must be identified and targeted. This concept may be applicable to the case presented here, but still, the existence of a true oligometastatic state remains controversial and this view point is not shared by all clinicians. In metastatic colorectal carcinoma, 40-70% of cases spread to the lymph nodes first but the liver is often the first distant site of spread, due to drainage of the intestine via the portal venous system [12]. Spread to the lungs can occur via direct drainage of rectal carcinoma through the inferior vena cava and thereafter other sites like the bones and brain may become involved [2]. However, involvement of sites like the skin, breast and axilla is extremely rare and may be associated with particularly aggressive subtypes of colorectal carcinoma (BRAF-mutant cases for example) [15]. Therefore, the majority of the data guiding the optimal approach to treatment in these cases is limited to information provided by published case reports.

The successful treatment of colorectal cancer with liver or pulmonary metastases is extensively described in the surgical literature. With liver-only metastases, approximately 20-25% of patients can achieve disease-free survival of over ten years [1]. The role of a multidisciplinary team approach is crucial here to determine the ideal treatment strategy for these patients, especially when surgery can be combined with ablative therapies including systemic chemotherapy, radiofrequency or microwave ablation or intra-arterial chemotherapy among others. The National Comprehensive Cancer Network (NCCN) recommends that patients with resectable

synchronous liver and/ or lung metastases can undergo resection and/ or local ablative therapies, although resection is preferred [9]. In colorectal cancer with isolated pulmonary metastases amenable to treatment with curative intent, surgical resection can lead to five-year survival of 45-65% [1]. However, the treatment of metastases to the breast and axilla is complicated and the selection of the optimal strategy depends on the primary tumour, involvement of other sites and the overall condition of the patient. Barthelmes et al suggested against surgical excision in these cases due to the underlying disseminated state of disease, predicted short life expectancy and the risk of tumour seeding onto the skin [10,16]. Others, like Fernandez de Bobadilla, suggest that excision can help to achieve local control of disease and prolong survival when combined with systemic chemotherapy [17].

Because of the rarity of this phenomenon, however, there is no high level evidence supporting an ideal approach and this decision is often made on a case-based approach [12]. In the case described here, the decision to proceed with surgical excision of isolated rare distant metastases was influenced by the fact that the patient had approached four-year survival with isolated metastases only and maintained a good quality of life despite this. She will continue to be surveyed for future metastases as well as her overall outcome.

Conclusion

Systemic therapies are standard aspects of treatment of various metastatic malignancies and traditionally were the only options for treating metastatic colorectal carcinoma. However, modern advances in science and technology have allowed improved survival and in some cases, cure, for select patients with metastatic colorectal cancer. This has been clearly demonstrated in cases of metastases to the liver and lungs, but metastases to the skin, breast or axilla are so uncommon that there is currently no general consensus regarding the best treatment options for these patients. Treatment decisions here are often made based on multidisciplinary discussions and information derived from published case reports or series. A decision to perform excision or provide systemic treatment of isolated metastases to these areas is also derived from the concept of an oligometastatic versus micrometastatic disease state. In the oligometastatic state, the presence of small diffuse metastases (micro metastases) is inherently denied and theoretically, local excision or ablative therapies should be sufficient to control the extent of disease and possibly provide a cure. However, success in treating cases like this relies on the fact that primary tumour biology influences its metastatic potential. This explains why some patients can achieve cure of their disease even if initially considered unresectable at diagnosis. But it also explains why overall cure rates have not significantly improved although several advances in treatment have occurred over the years. Colorectal cancer metastases to the skin, breast and axilla

are extremely rare and based on the published literature generally signify a poor prognosis. However, limited metastatic potential, as perhaps described in this case, may show that local therapeutic options, including surgical excision, may improve quality of life and survival.

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