The Elusive Primary: Metastatic Adenocarcinoma of the Breast Presenting Solely as a Hard Sternal Mass

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Patient: Female, 62-year-old
Final Diagnosis: Metastatic adenocarcinoma of the breast
Symptoms: Mass at the sternum
Clinical Procedure: Biopsy of the sternal mass
Specialty: Family Medicine • Orthopedics and Traumatology • Surgery

Objective: Unusual clinical course
Background: Carcinoma of unknown primary (CUP) is a diverse category of malignancies diagnosed in patients who have metastatic disease but without an identifiable primary tumor at initial presentation. We report a case of CUP which was later diagnosed to be metastatic adenocarcinoma of the breast in a 62-year-old woman. The patient initially presented to a primary care clinic with an incidental finding of a small hard mass in the middle of the sternum, with no other clinical findings in the breast or axillary lymph nodes. Chest X-ray, ultrasound, and CT scan of the sternum suggested a benign sternal lesion, and a mammogram was normal. Due to the persistence of the mass, a biopsy was performed. The histopathological findings revealed a metastatic adenocarcinoma, most likely from breast origin, with positive estrogen receptor (ER) and mammaglobin on immunohistochemistry studies. The patient subsequently underwent PET scan, repeat mammogram, and MRI of the breast. Following high uptake in the rectum on PET, a colonoscopy was performed, revealing a suspicious rectal mass. The mass was surgically excised, and the final histopathological examination concluded the mass was a second primary adenocarcinoma of the rectum. Genetic analyses for BRCA1 and BRCA2 were negative.

Conclusions: This is a rare case of an isolated bone-like lesion on the sternum due to metastatic adenocarcinoma of the breast in a patient with no prior history of breast cancer and lacking any clinical or radiological evidence of breast or axillary lymph node lesions on presentation. The patient was also subsequently diagnosed with 2 primary carcinomas. Thorough clinical examination, extensive radiological investigations, laboratory investigations, histopathological examination, and a multidisciplinary approach are essential in managing CUP.

Keywords: Adenocarcinoma • Breast Neoplasms • Neoplasms, Unknown Primary • Sternal

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Background

Cancer of unknown primary (CUP) is a diverse category of malignancies diagnosed in patients who have metastatic disease, but an identifiable primary tumor remains elusive despite a thorough initial evaluation [1]. CUP could be from multiple heterogeneous cancer origins with a wide range of clinical manifestations [2]. It is the third-to-fourth most common cause of death from a cancer-related condition [3]. Patients with CUP are usually diagnosed at 60-75 years old [4]. CUP accounts for approximately 3-5% of all cancer cases worldwide [5]. CUP has a poor prognosis, with a median survival rate of less than 1 year [6]. The survival rates of CUP can be divided into 2 prognostic outcomes depending on the clinicopathological characteristics. Most patients have an unfavorable prognosis, with a survival rate of 3-6 months despite optimum treatment with a variety of chemotherapies, while the 15-20% of patients have a favorable prognosis that results in an average survival of 10-16 months, with long-term disease control in 30-60% of cases [7].

Chest wall lesions, both benign and malignant, make up approximately 5% of all thoracic tumors. The mass found could be soft, suggestive of soft tissue, fat, or fluid-containing lesion, or firm, suggestive of a calcified or ossified lesion. Differential diagnoses of a hard sternal mass include fibrous dysplasia, myositis ossificans, tumoral calcinosis, osteochondroma, chondrosarcoma, or osteosarcoma [8]. In the context of breast cancer, the presence of sternal or parasternal swelling is usually a clinical indicator of advanced internal mammary chain (IMC) node involvement [9]. Due to the anatomical position, these lymph nodes are not palpable on clinical examination and their involvement is usually found on radiological investigation or surgical intervention for a known breast cancer case [10].

We report a rare case of metastatic adenocarcinoma of the breast with an isolated hard sternal mass as the sole primary presentation, without clinical or initial radiological evidence of axillary and thoracic lymph nodes or any breast lesions. The patient was also subsequently diagnosed with a synchronous primary rectal adenocarcinoma, which suggested multiple primary cancers (MPCs). MPCs are defined as the presence of 2 or more tumors that have no relation to one another and have developed from different organ sites at the same or different times [11]. Within 20 years of follow-up, the incidence of MPCs in a cancer population ranges from 2.4% to 8% to 17% [12]. The prognosis of MPCs is poorer than single primary tumors [12]. MPCs’ exact cause is not yet fully understood, but the immune system of patients, genetic vulnerability, and chemotherapy and radiation therapy used to treat cancers are some of the most frequent causes of MPCs [13].

This case report emphasizes the importance of keeping a high level of suspicion and low threshold for a tissue diagnosis, even when a condition has been reported as “benign or no malignancy” as this could potentially delay the diagnosis. This report also discusses the difficulties in making the correct diagnosis; thus, the need for a thorough investigation and the essential support from a multidisciplinary team (MDT).

Case Report

A 62-year-old woman presented for her routine dyslipidemia and type 2 diabetes mellitus follow-up in a primary health care clinic in October 2019. During the consultation with a primary care physician, she reported she had a mass in the middle of her chest that had been discovered while she was taking a bath 1 week before the visit (Figure 1). The hard bony mass was not increasing in size.

The patient was otherwise well. She had no chest pain, cough, difficulty breathing, or other cardio-respiratory symptoms. She also had no other palpable masses or breast lumps, and no loss of weight or loss of appetite. On further questioning, the patient had no history of altered bowel habits, tenesmus, per rectal bleeding, melena, or hematochezia. She has no family history of breast cancer, ovarian cancer, or colon cancer, and had no history of taking any contraceptive pills or hormonal replacement therapy. She attained menarche at age 12 years and menopause at age 50 years. She had 5 children. Her first childbirth was at 28 years old and her last childbirth was at age 37 years. She breastfed each of her 5 children for

Figure 1. The original position of the bony lesion and well-healed scar of post-surgical excisional biopsy in the middle of the sternum. The patient also had a fungal infection under the breasts, which was treated successfully. Arrow indicates the lesion.
a minimum of at least 1 year. She had diabetes mellitus for 2 years and her diabetes mellitus control was within normal limits on Metformin XR 500 mg ON.

On examination, the patient was afebrile. She was a medium-built woman with a BMI of 29 kg/m². Her blood pressure was 126 mmHg systolic, and 70 mmHg diastolic. Her pulse rate was 70 beats per minute. Breast examination revealed no overlying skin changes, palpable mass, or nipple discharge. She had no palpable axillary, supraclavicular, and cervical lymph nodes. Examination of the middle chest revealed no overlying skin. It was not mobile, was bony-hard in consistency, round in shape with an ill-defined border, and measured 2 cm in diameter. There were no overlying skin changes and no punctum seen.

A chest X-ray revealed a lobulated soft-tissue opacity around the lower sternum, which could only be appreciated on the lateral projection (Figure 2). There were no obvious signs of bony erosions of the sternum seen on a plain radiograph. There was also no other lesion at the lung parenchyma. Ultrasonography of the mass revealed a well-defined, heterogeneously hypoechoic lesion on the chest wall over the left fifth costosternal joint, measuring 1.2×1.6×1.5 cm (AP×W×CC). There was no surrounding fat streakiness or underlying sternal erosion seen. The underlying pectoralis muscle area was intact and normal. The thyroid and lung fields were normal (Figure 3). A mammogram was also done and reported as normal, with breast imaging reporting of BIRADS 1. There was no significant internal mammary or bilateral axillary lymph nodes seen on the series of imaging.

The patient was then referred and seen by the orthopedic surgeon within 1 week of the CT scan findings. However, she was then treated conservatively and given an appointment to be seen again in 6 months. Unfortunately, the COVID-19 pandemic hit the region, and due to logistic issues imposed by the pandemic, when she had to return to her hometown located in a different state, the patient was not able to come for the appointment.

Ten months after the initial presentation, she went to the nearest hospital in her hometown to seek a second opinion. The size of the mass remained the same. She was seen by a general surgeon, who decided to do an excisional biopsy of the mass. There was no irradiation or intervention done to the sternal mass area after the excisional biopsy.

The histopathological examination of the sternal mass revealed that the dermis was infiltrated by malignant cells arranged in a glandular and cribriform pattern with occasional tumor nests and cords. The cells displayed mild-to-moderate nuclear pleomorphism, vesicular chromatin, small nucleoli, and moderate cyttoplasm. Mitosis was occasionally seen and the stroma was desmoplastic. The tumor cells were seen infiltrating into the adipose tissue and in between the skeletal muscle bundles. Perineural invasion was also present. However, there was no lymphovascular invasion noted. Immunohistochemistry findings revealed that the cells were diffusely and strongly positive for cytokeratin (CK7), estrogen receptor (ER), and mammaglobin. CK 20 was focal and weak. They were negative for thyroid transcription factor 1 (TTF1) and paired box gene 8 (PAX8) (Figure 4). The final interpretation of the biopsy was metastatic adenocarcinoma.

Given the histopathological findings from the biopsy, a repeat mammogram with ultrasound of bilateral breasts was done. The result showed evidence of an ill-defined lobulated peri-ductal hypoechoic lesion at 8-9 o’clock of the peri-areolar region, measuring 0.6×1.8×1.7 cm. The final impression was a highly suspicious right-breast peri-ductal lesion with regional ductal dilatation (BIRADS 5). The surgical team proceeded with an ultrasound-guided biopsy of the right-breast lesion but found no evidence of intraductal proliferation, cytological atypia, in-situ, or invasive carcinoma. The final interpretation of the right-breast biopsy was benign sclerotic breast tissue.
Because of the uncertainties in the diagnosis of breast cancer, she decided to consult her primary care physician 3 months after the initial biopsy and was subsequently referred to another surgeon under a surgical endocrine team within the same month for further evaluation. During this visit, the previous sternal mass biopsy had been re-examined by another histopathologist with added immunohistochemical stains that were positive for CK7, G-A-T-A nucleotide sequences (GATA3), ER (>90%), and progesterone receptor (PR) (40%). However, the cells were negative for c-erbB-2 and CK20. The features were consistent with metastatic adenocarcinoma, likely primary from the breast.

MRI of the bilateral breast at this stage showed a right retroareolar dilated duct with no intraductal lesion seen (BI-RADS 4B or moderate suspicion) and with no significant axillary lymph nodes detected at both breasts. A repeated right-breast biopsy was done and revealed the same result as the first reported right-breast biopsy, which was benign sclerotic breast tissue. A PET scan done for cancer surveillance showed an irregular F-fluorodeoxyglucose (FDG)-avid focus lesion at the mid-rectum measuring 2.9 cm (AP)×3.0 cm (W)×3.2 cm (CC) in metabolic sizes with standardized uptake values (SUVs) max 38.5. The impression was a suspicious mitotic lesion due to the irregular hypermetabolic focal lesion at the mid-rectum. However, there was no evidence of hypermetabolic lesions at the breasts and anterior chest wall seen. There were no other FDG-avid lymph nodes or abnormally increased FDG activity elsewhere.

To confirm the presence of the rectal lesion, an MRI pelvis and a colonoscopy were done. The result showed that there was an enhancing fungating mass, which appeared to arise at the 10-2 o’clock position of the low rectum, approximately 4.3 cm from the anal verge and 1.5 cm from the anorectal junction, with nodal involvement. The colonoscopy biopsy revealed high-grade dysplasia of lower-rectal cancer. Immunohistochemistry

Figure 3. Computed tomography (CT) scan findings of the sternal mass. (A1, A2) sagittal views (B) axial view (C) coronal view. Arrow indicates the lesion.
stains of the tumor cells were positive for caudal-type homeobox transcription factor 2 (CDX2) and CK20, which strongly supported intestinal differentiation but negative for ER, CK7, and GATA3. This report suggested that the rectal cancer was primary in origin.

This case became more complex with the incidental findings of the high-grade dysplasia of lower-rectal cancer and uncertainties in the finding of benign sclerotic breast tissue, which required a multidisciplinary team (MDT) approach that consisted of an endocrine surgeon, colorectal surgeon, radiologist, oncologist, pathologist, and primary care physician.

The MDT meetings reached several consensuses. Firstly, even though the rectal biopsy showed a high-grade dysplasia, it was felt that the actual carcinoma area was missed during the biopsy. It was decided to treat the mass as malignant in view of its highly suspicious appearance. Secondly, in view of the IHC features of the rectal biopsy that pointed towards an intestinal origin, it was decided to treat the rectal mass as a second primary. Thirdly, given that the active disease on the PET scan was in the rectum, this was given priority to be treated first. Fourthly, with sternal metastases, the breast cancer was essentially a stage IV disease, so it was decided that neither mastectomy nor breast radiotherapy was validated. The patient was also not keen for any surgery to the breast or sternum.

Therefore, she was subjected to radical treatment of her rectal cancer following the standard RAPIDO protocol with short-course radiotherapy of 25 Gy in 5 fractions, followed by 9 cycles of neoadjuvant FOLFOX chemotherapy regimen and laparoscopic-assisted ultra-low anterior resection with covering.

Figure 4. (A) Section of the sternal mass shows intradermal malignant cells infiltration arranged in glandular and cribriform patterns (H&E 40×). (B) The cells display mild-to-moderate nuclear pleomorphism, vesicular chromatin, prominent nucleoli, and eosinophilic cytoplasm (H&E, 200×). The tumor cells are positive for (C) CK7, (D) estrogen receptor (ER), and (E) mammaglobin.
ileostomy. The final pathological report for the surgical resection of the rectum revealed minimal residual adenocarcinoma of the rectum, moderately differentiated, and the tumor was staged as ypT1N0 as per ypTNM AJCC staging, with negative circumferential margin. The final IHC of the specimen confirmed that the rectal adenocarcinoma was a separate primary from that of the breast carcinoma. The possibility of Lynch syndrome was also considered. Fortunately, the genetic testing for BRCA1 (Breast Cancer gene 1) and BRCA2 (Breast Cancer gene 2) showed no abnormal mutations.

She was initially given adjuvant capcitabine following the surgery, but this was poorly tolerated. She is currently on tamoxifen for her underlying metastatic adenocarcinoma of the breast, with a future plan of reversal of her ileostomy. She will continue to be under close surveillance by an oncologist, breast surgeon, and colorectal surgeon, with periodic imaging and colonoscopy. Currently, it has been more than 3 years since the sternal mass was detected and her cancers seem to be in remission.

Discussion

We reported a rare case of carcinoma of unknown primary (CUP) that initially presented as a hard sternal mass at a primary care clinic. To date, there are few reported cases of isolated presentation of a sternal mass as the sole manifestation of metastatic adenocarcinoma of the breast, with no clinical or radiological evidence of breast lesions or lymph nodes at initial presentation.

A diagnosis of occult breast cancer (OBC) may be considered, although it usually presents as axillary lymph node (LN) metastases in the absence of a primary breast tumor on clinical evaluation or radiography [14]. OBC makes up 0.3% to 1.0% of all breast cancers [15]. A literature search revealed a case reported by Mu et al of a possible OBC presenting as a mediastinal mass in a middle-aged woman [16]. The case was the first to suggest a possibility of OBC presenting with a sternal mass instead of the usual lymph nodes presentation. The clinicopathological characteristics of OBC, such as lymph node metastasis and immunohistochemistry – for example, hormone status/human epidermal factor receptor-2 (HER-2) status – are required to aid in the diagnosis of OBC [17]. According to the American College of Radiology, MRI is needed for OBC patients who do not demonstrate any primary breast lesion on clinical evaluation or routine radiological examination, especially on mammogram and ultrasound [18]. Fluorodeoxyglucose (FDG) positron emission tomography (FDG PET/CT) has been reported to detect OBC when it was not detected by other modalities [19].

A systematic approach to histopathological examination is crucial in managing CUP. The initial step is a histomorphological evaluation by conventional light microscopy, followed by judicious use of ancillary studies such as immunohistochemistry and molecular analysis [20]. Immunohistochemistry (IHC) has become an important tool to objectively support histologic diagnoses of some difficult cases. There is no single IHC marker that is fully sensitive and specific for a particular tumor; therefore, a panel of IHC markers is strongly recommended and several algorithms have been proposed. Cytokeratin (CK) is an epithelial marker and is expressed in tumors with epithelial differentiation. A coordinate expression of CK7 and CK20 aids to classify the tumors into subsets of carcinomas and are regarded as the first panel of IHC. Breast adenocarcinomas are usually CK7+/CK20−, whereas rectal adenocarcinomas show a CK7-/CK20+ profile [20]. A second panel of IHC markers may be considered to further refine and narrow the diagnosis [21]. As in our case, morphological features confirm adenocarcinoma with CK7 positivity, and hence, a limited second IHC panel was chosen. The estrogen receptor is expressed in about 60% of breast cancer, whereas mammaglobin is specific for breast cancers [22]. Our patient showed immunoreactivity to both markers. The revised biopsy with added IHC staining was positive for CK7, GATA3, ER (>90%), and PR 40%, which are features consistent with metastatic adenocarcinoma, likely primary from the breast. On the other hand, the rectal adenocarcinoma was negative for these breast markers [20].

The tissue biopsy in this case also showed no evidence of ectopic breast tissue (EBT). EBT is also known as accessory or supernumerary breast tissue. For this patient, there was no normal breast tissue seen in the biopsy of the sternal mass. To consider an EBT, features of breast tissue must be seen in the HPE. The clinical presentation of EBT usually appears as a diffuse soft-tissue mass that can be seen anywhere along the “milk-line” as a result of failure of embryonic development, with the axilla being the most often reported site [23]. Considering the embryonic development, the sternum is an atypical site for the occurrence of EBT.

With given the clinical information, histomorphological features, and interpretation of IHC markers, the final diagnosis was metastatic adenocarcinoma, likely from breast origin. As a sternal mass as a sole presentation of metastatic adenocarcinoma of breast origin is a rare condition, the treatment was considered based on available suggested treatment for CUP due to OBC. Although there is no published standard treatment protocol, a few treatment interventions have been recommended, including surgery, radiotherapy, and hormonal biological therapy [24]. In previous years, the mainstay of treatments for OBC included ipsilateral mastectomy and axillary lymph node dissection (ALND). However, as time goes by with more intervention, breast-conserving therapy (BCT) has become the trend for the current treatment practice [25].
most recent National Comprehensive Cancer Network (NCCN) guidelines suggested that individuals with negative MRI results should receive breast radiation therapy or mastectomy combined with axillary LN dissection (ALND), and those with stage II or stage III diseases should receive systemic chemotherapy hormonal treatment [26]. However, as our case was that of non-regional metastases of adenocarcinoma of the breast, and the presence of sternal or parasternal swelling is usually a clinical indicator of advanced internal mammary chain (IMC) node involvement, the management algorithm follows that of a stage IV breast cancer. Generally, surgery is not recommended in stage IV breast cancer as it has failed to show survival benefits, although it can be done with palliative intent in patients with a fungating breast mass [27]. Furthermore, in the absence of BRCA mutation, it was difficult to recommend bilateral mastectomy in our patient. It was decided that the hormonal blockade with tamoxifen was sufficient for her ER-positive breast cancer, since the disease appeared to be in remission on PET following excision of the sternal mass.

Unfortunately for the patient, she had metastatic adenocarcinoma, likely from breast origin, and primary rectal cancer that occurred simultaneously, which is in accordance with the diagnosis of multiple primary carcinosomas (MPCs). OBC and rectal cancer occurring simultaneously are extremely uncommon tumors and a literature review revealed only 1 reported case, by Özlem et al in 2019 [28]. The challenge in managing MPC, especially when they present synchronously, is to decide which primary to treat first, as the cancers most often require different treatment modalities. The decision often requires input from various different multidisciplinary teams involved in the patient’s care. In our patient, her breast cancer required tamoxifen while her rectal cancer required radiotherapy, chemotherapy and surgery. The FOLFOX chemotherapy combination (oxaliplatin, leucovorin, and 5-FU) has been a standard treatment for adenocarcinoma, likely from breast origin, and primary rectal cancer that occurred simultaneously, which is in accordance with the diagnosis of multiple primary carcinosomas (MPCs). OBC and rectal cancer occurring simultaneously are extremely uncommon tumors and a literature review revealed only 1 reported case, by Özlem et al in 2019 [28]. The challenge in managing MPC, especially when they present synchronously, is to decide which primary to treat first, as the cancers most often require different treatment modalities. The decision often requires input from various different multidisciplinary teams involved in the patient’s care. In our patient, her breast cancer required tamoxifen while her rectal cancer required radiotherapy, chemotherapy and surgery. The FOLFOX chemotherapy combination (oxaliplatin, leucovorin, and 5-FU) has been a standard treatment for colorectal cancer in recent years [29]. It was decided to treat her rectal cancer first in view of this being the active disease. It was also hoped that 5-fluorouracil used for her colorectal cancer occurring simultaneously with the metastatic adenocarcinoma of the breast. This is also extremely uncommon. A multidisciplinary team (MDT) approach is important due to the complexity of the case presentation. In summary, the case presented in this report is unique and adds to the existing body of knowledge on CUP, uncommon presentation for metastatic adenocarcinoma of the breast, possible new presentation of an OBC, and MPCs.

Regarding genetic risks, a study reported the relationship between genetic predisposition and synchronous tumors [30]. By definition, a synchronous primary tumor occurs when 2 different tumors that both developed in the same patient are found within 6 months [30]. The patient had no family history of cancer and the diagnosis of a second tumor was made more than 1 year after the first presentation.

The presence of BRCA1 and BRCA2 genes is the most common cause of genetic inheritance of breast and ovarian cancer [31]. When compared to BRCA-negative patients, those who have BRCA1 and BRCA2 mutations have a worse prognosis of breast cancer. The survival rate of BRCA1 carriers is lower than that of BRCA2 patients [32]. However, for this patient, her BRCA1 and BRCA2 genes were negative.

**Conclusions**

This was a rare case of an isolated bone-like lesion on the sternum as a sole presentation of metastatic adenocarcinoma of the breast. A thorough history-taking, physical examination, and investigations were crucial in determining the primary lesion for the best treatment decision. Because of the rarity, regular monitoring and a high level of suspicion are needed to avoid a delay in diagnosis that could result in a delay in treatment. The patient also had rectal cancer that occurred simultaneously with the metastatic adenocarcinoma of the breast. This is also extremely uncommon. A multidisciplinary team (MDT) approach is important due to the complexity of the case presentation. In summary, the case presented in this report is unique and adds to the existing body of knowledge on CUP, uncommon presentation for metastatic adenocarcinoma of the breast, possible new presentation of an OBC, and MPCs.

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**Declaration of Figures’ Authenticity**

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