An unusual case of isolated, serial metastases of gallbladder carcinoma involving the chest wall, axilla, breast and lung parenchyma

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Abstract

In the English literature, only 9 cases of adenocarcinoma of the gallbladder with cutaneous metastasis have been reported so far. One case of multiple cutaneous metastases along with deposits in the breast tissue has been reported. We present a case of incidental metastatic gallbladder carcinoma with no intra-abdominal disease presenting as a series of four isolated cutaneous right chest wall, axillary nodal, breast, and pulmonary metastases following resection and adjuvant chemoradiation for her primary tumor. In spite of the metastatic disease coupled with the aggressive nature of the cancer, this patient reported that her energy level had returned to baseline with a good appetite and a stable weight indicating a good performance status and now is alive at 25 months since diagnosis. Her serially-presented, oligometastatic diseases were well-controlled by concurrent chemoradiotherapy and stereotactic radiation therapy. We report this case study because of its rarity and for the purpose of complementing current literature with an additional example of cutaneous metastasis from adenocarcinoma of the gallbladder.

Introduction

Cutaneous metastases associated with a visceral malignancy are fairly uncommon. Estimates from previous studies and case reports indicate that 0.7-9% of internal malignancies metastasize to the skin. Breast cancer is the most common malignancy noted to develop dermal metastases up to approximately 24%. This is followed by an estimated 3-4% occurrence from cancers of the lung, colon, kidney, ovaries and urinary bladder.12

Metastatic cancer involving cutaneous tissue is not unusual, but the incidence of cutaneous metastases from an adenocarcinoma of the gallbladder is still very rare. Since 1956, only 9 cases of gallbladder cancer metastasizing to the skin as multiple nodules have been reported in the English literature. The likely route of dissemination to sites of metastasis is via the venous system and lymphatic channels, but it may spread to the skin by extension directly from involvement of the liver and peritoneum.12 In this paper, we report a new case of a solitary right chest wall cutaneous metastasis, subsequent axillary lymph nodal, breast, and lung metastases of gallbladder cancer without active disease evident in the abdomen or at the original site of occurrence within the gallbladder fossa.

Case Report

A 74 year old woman initially presented to her local emergency department in October 2010 with symptoms ofnausea, abdominal pain and chills. A computed tomography (CT) scan of the abdomen and pelvis as well as an ultrasound of the liver were performed and revealed gallstones and a possible mass within the gallbladder. She then proceeded to surgery with a laparoscopic cholecystectomy performed at an outside institution. The operative note indicated the gallbladder was acutely inflamed and distended. Review of the pathology specimen revealed invasive grade 2 (of 4) adenocarcinoma, forming a 3.5x2.5x1.3 cm mass in the gallbladder arising in a background of dysplasia. The tumor was found to extend through the gallbladder wall and into the pericystic soft tissue but not involving the surgical margin. Perineural invasion was noted. There was no indication that lymph nodes in the region were dissected or noted in the outside pathology report.

Two weeks after surgery, the patient presented to Mayo Clinic for a second opinion. A repeat CT scan of the abdomen and pelvis was obtained and demonstrated changes consistent with an interval cholecystectomy. In addition, just posterior to the liver, a small radio density was noted, which was felt to be a possible dropped gallstone from the previous surgery. A small fluid collection was noted in the gallbladder fossa with stranding in the adjacent fat. There was no evidence of hepatic metastases. A CA19-9 level obtained at that time was elevated at 198 U/mL. Approximately one month following the initial surgery, the patient underwent a staging laparoscopy followed by excision of the previous periumbilical port, with excision of the remaining port sites and a subsequent bisegmentectomy of segments 4B and 5 of the liver along with a regional hepatoduodenal ligament lymphadenectomy and excision of the cystic duct stump. Review of the surgical specimen did not reveal any evidence of residual disease in the previous surgical bed or in the surgical port sites. However, the hepatoduodenal lymphadenectomy revealed a single (of 11) hepato-duodenal lymph node was positive for metastatic adenocarcinoma.

The patient recovered well from surgery and reported having a very good appetite, stable weight, and a good energy level. A repeat CA19-9 level obtained at that time had returned to within normal range at 14 U/mL. She then proceeded with adjuvant therapy and went on to receive two cycles of weekly gemcitabine chemotherapy followed by chemoradiation to the gallbladder fossa and lymph node regions at risk. Continuous venous infusion 5-fluorouracil (5-FU) chemotherapy was given during radiotherapy. She received 4500 cGy of radiation therapy in 25 fractions using a six-field technique with a boost of 540 cGy in 3 fractions to the gallbladder fossa operative bed for a total dose of 5040 cGy. Following recovery from chemoradiation, the patient went on to receive two more cycles of gemcitabine chemotherapy.

During her final cycles of gemcitabine chemotherapy, the patient noted a small enlarging lump on her right lateral chest wall at the level of her bra line. The lump was initially soft and painless, but it became more firm and painful over time. Of note, her CA19-9 level had remained within normal range at 21 U/mL. Due to concerns for metastasis, an incisional biopsy of the right chest wall mass was performed at an outside institution approximately one month after completion of adjuvant therapy. The mass was found to be a recurrence of her gallbladder cancer. A PET scan obtained at that time demonstrated a 1.7 cm hypermetabolic nodule in the right chest wall (Figure 1A). Approximately three weeks after the incisional biopsy, the patient returned to Mayo Clinic and underwent a wide local excision of the area. Review of the surgi-
cal specimen revealed metastatic adenocarcinoma consistent with gallbladder primary, forming a 1.8x1.8x1.0 cm mass, with tumor present at 0.3 cm from the closest margin (Figure 2A). The patient was then referred back to radiation oncology for consideration for treatment. Mammography of both breasts performed did not reveal any malignancy. Since it was felt that the cancer recurrence was an unusual pattern for this type of cancer, adjuvant radiotherapy and chemotherapy were not recommended at that time.

The patient did well following resection of her right chest wall metastasis. About five months after her chest wall resection, the patient complained of a new painful lump in her right axilla. This was found to be intensely avid on PET scan and measured approximately 3 cm (Figure 2B). There was no evidence of other distant metastatic disease. Her CA19-9 level had risen to 619 U/mL. Therefore, she was taken to surgery for a right axillary lymph node dissection the following day. Review of the pathology specimen revealed metastatic adenocarcinoma consistent with a gallbladder primary, forming a 3.6x3.0x3.0 cm mass, with focal extra capsular extension into surrounding adipose tissue but was completely excised with negative margins. The patient was then referred back to her medical and radiation oncologists for consideration of adjuvant treatment. At one month post-surgery, this now 76-year-old woman went on to receive daily radiotherapy along with twice daily oral capecitabine chemotherapy on the days she received radiation therapy. She received 4400 cGy over 22 fractions with a 600 cGy boost in 3 fractions to the operative bed for a total dose of 5000 cGy to the right axilla. At a two-month follow up visit status post adjuvant treatment, the patient felt well, reported a good appetite, and some weight gain. She noted only occasional tenderness with palpation of her right lower anterior rib cage approximately at the mid-clavicular line and some soreness in her right axilla but no new lumps. A CT scan of the chest, abdomen, and pelvis was obtained revealing complete resolution of the mass in the upper right axilla with mild soft tissue stranding. Unfortunately, a new bi-lobed nodule had developed in the low right axilla region concerning for a possible recurrence of metastatic gallbladder cancer possibly involving a new lymph node. There was no other lymphadenopathy noted. There were no signs of recurrence in the abdomen or pelvis and the liver was negative for metastases. Her CA19-9 level was within normal range at 26 U/mL. On follow up, a repeat CA19-9 level was found to be elevated at 77 U/mL. A PET scan demonstrated two new hypermetabolic right axillary nodules which both had slightly increased in size com-

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**Figure 1.** Computed tomography-positron emission tomography showing: A) an axial view of the very first cutaneous metastatic deposit to the right chest wall 10 months after the initial diagnosis; B) an axial view of the second cutaneous metastasis involving right axillary lymph nodal mass five months after the initial right chest wall metastasis or 15 months after the initial diagnosis; C) an axial view of the 1 cm superomedial recurrent right axillary/chest wall lymph node; D) an axial view of the 1.7 cm inferior and lateral recurrent right axillary/chest wall lymph node noted. Both 1C and 1D images are of metastases that occurred five months after the second occurrence and 20 months after the initial diagnosis. These are also shown in Figure 3.

**Figure 2.** Haematoxylin & Eosin stain of tumor tissue from the first site of metastatic disease on the right chest wall (A) and of the right axilla/chest wall node metastases (B).

**Figure 3.** Computed tomography-positron emission tomography showing a coronal view of recurrent metastatic right axillary/chest wall lymph nodes five months after the second occurrence of cutaneous metastatic disease and 20 months after the initial diagnosis.
pared to the previous CT scan obtained one month prior and was worrisome for metastatic disease (Figure 3). The first superomedial lesion measuring 1 cm was noted superomedial to the lower axillary nodule and abutted the right chest wall in the breast tissue at the lateral fourth rib without definite bony invasion (Figure 1C). A second nodule in the right axilla inferior and lateral to the first nodule measured 1.7 cm (Figure 1D). These lesions appeared to be in transit lymphatic metastases. There were no additional foci of PET-avid disease or any evidence of distant metastatic disease. It should be noted that these lesions were just inferior to the prior radiation treatment field. The patient then underwent a wide local excision of the mass involving the right breast tissue, but the chest wall lesion was subtotally resected leaving positive margins. Comparison was made of the tumor tissue from this biopsy with the biopsy specimen from her second right chest wall occurrence and confirmed the presence of morphologically similar gallbladder carcinoma (Figure 2B). Immunohistochemical staining confirmed the diagnosis, staining positive for keratin 7 (Figure 4A) and negative for keratin 20, estrogen receptor (Figure 4B), progesterone receptor, CDX 2, mammaglobin & GCDFP15.

In view of positive margins, she was offered additional local regional radiotherapy to a planned dose of 5000 cGy to the postoperative bed/right chest wall using intensity modulated radiation therapy planning due to the proximity of her previous radiation treatment field along with radiosensitizing chemotherapy with oral capcitabine. She tolerated this treatment well and had no concerns or new lumps at the end of treatment.

Two months later, routine surveillance revealed a new left upper lung nodule on a CT scan. The round nodule measured 8 mm in size, and was thought to be related to her primary gallbladder carcinoma (she is a lifelong non-smoker). A follow-up PET/CT scan showed moderate to intensely avid FDG uptake in this nodule, with a SUV maximum of 4.6. Importantly, the patient had no other abnormal uptake elsewhere in her body to indicate additional sites of metastatic disease, including previously treated sites. A biopsy was not performed due to the invasive nature of the procedure (risk of pneumothorax). The patient received stereotactic body radiotherapy (SBRT) to this isolated metastasis. The SBRT dose was 5400 cGy in 3 fractions, administered every other day (Figure 5). The patient tolerated the procedure well, and remained asymptomatic with high performance status as an outpatient. Close continued surveillance was recommended.

Discussion

Current epidemiological data show carcinoma of the gallbladder to be the sixth most common cancer involving the gastrointestinal region. It was even described as early as the late 1700’s. There has been an association of gallbladder cancer and a history of gallstones. Seventy-five percent of gallbladder cancer patients have a history of cholelithiasis. Patients with gallstones have a four to five fold increased risk of developing gallbladder cancer than patients without cholelithiasis. Unfortunately, this disease is still likely to present at an advance stage and without an effective treatment. Patients with advanced gallbladder cancer are known to have a poor prognosis with only a 10% one-year survival rate. Those with localized lesions are estimated to have a five-year survival rate of only 32%. Gallbladder carcinoma continues to be more prevalent in woman greater than 65 years of age, and it has a three-fold higher prevalence in woman over men with a peak occurrence in the seventh decade of life.

The occurrence of gallbladder cancer is rare, usually presenting with symptoms consistent with benign disease. The most common presenting symptom is abdominal pain in the right upper quadrant. Patients with advanced disease are more likely to have nausea, vomiting, anorexia, weight loss, jaundice and a palpable mass. Even with advanced diagnostic imaging, carcinoma of the gallbladder is more likely to be diagnosed at a later stage and having metastasis in up to a third of these patients. It is even rarer for metastasis to go to extra abdominal sites such as the skin as in our case study patient. In patients undergoing laparoscopic surgery, there is concern regarding seeding of cancer cells at port sites or even along the track of a needle biopsy. In our patient, excision of peri-umbilical port sites following her initial surgery did not reveal any tumor. Yet, she eventually presented with a dermal metastasis.

Our case study patient had a cutaneous metastasis to the right lateral chest wall that occurred when there was complete control/remission of the intra-abdominal disease. The involvement of a right axillary lymph node can be explained in terms of regional nodal drainage. Isolated single cutaneous metastasis and an oligo-metastasis to the lung parenchyma from gallbladder carcinoma with complete remission/control of primary disease has not been reported so far in the English literature. SBRT treatment for isolated or oligometastatic disease to the lung parenchyma is highly effective.
Conclusions

In conclusion, there are limited examples of cutaneous metastatic gallbladder adenocarcinoma in the English literature. This case illustrates an unusual dissemination of gallbladder carcinoma. In spite of multiple recurrences of metastatic gallbladder carcinoma, even in the absence of intra-abdominal disease at the primary site of occurrence, our patient is alive and well 25 months following her initial diagnosis, having survived multiple oligometastatic recurrences involving multiple organs.

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