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Metastatic Breast Cancer Presenting as Acute Cholecystitis and Hyperbilirubinemia

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1. Abstract

Acute cholecystitis is one of the most common reasons for acute surgical intervention in the emergency setting [1]. Rarely, pathological examination of the surgical specimen reveals incidental gallbladder cancer and even more infrequently metastasis of gallbladder from a distant site. We present a case of a patient with a known history of inflammatory breast carcinoma, who presented with symptoms of right upper quadrant pain and jaundice and diagnostic work-up consistent with acute cholecystitis, subsequently found to have metastatic breast cancer to the liver and gallbladder.

2. Introduction

Inflammatory Breast Cancer (IBC) represents 1-2% of all invasive breast carcinomas and is associated with an underlying ductal or lobular primary tumor [2, 3]. This subtype of breast cancer presents as swelling and redness of the involved breast, with a characteristic peau d'orange look. IBC is a very aggressive subtype of breast cancer conferring a worse prognosis than non-inflammatory breast cancer, with a 5 year overall survival rate of 25.4% vs 31.8% respectively [4]. This is largely due to propensity for distant metastasis and local recurrence. 30% of patients with IBC had metastatic disease at the time of diagnosis compared to 6-10% of patients with non-inflammatory breast cancer [5, 6].

Common sites of metastasis for breast cancer are axillary lymph nodes, bone, lungs and pleura, liver and brain [7]. Breast cancer metastatic to the Gallbladder (GB) is a rarely reported phenomenon with less than 25 case reports found in the literature in the past

30 years [8]. Documented metastases to the GB from distant sites are very rare and most commonly found with malignant melanoma (<50 case reports), cervical carcinoma, renal cell carcinoma, and non-small cell lung cancer [9, 10, 11]. Only one case report of IBC metastatic to the GB was identified [12]. No case report of IBC metastatic to both liver and GB was identified in the literature.

We present a unique case of a 62-year-old female with a history of IBC and underlying mass of ductal histotype diagnosed 2 years ago, presenting with symptoms of cholecystitis and obstructive jaundice, diagnosed with metastatic breast cancer to the GB and infiltrative metastases to the liver after cholecystectomy.

3. Case History

The patient is a 62-year-old Caucasian woman who initially presented with acute erythema and edema of the left breast associated with a lump in 09/2018. Following biopsy and pathologic examination she was diagnosed with IBC T4dN1M0G3, stage IIIB, ER+, PR-, HER2+. She started neoadjuvant chemotherapy with tumor shrinkage but was unable to finish it due to intolerance of side effects. This was followed by modified radical mastectomy in August of 2019. 0/12 lymph nodes were positive. Margins were negative. Treatment plan was to start ado-trastuzumab emtansine (Kadcyla) and anastrozole. However, initially due to patient preference and later due to the COVID-19 pandemic, the patient was unable to start her treatment with Kadcyla.

In August of 2020, the patient presented to the emergency room three times for Right Upper Quadrant (RUQ) and epigastric pain,

nausea, and vomiting. She also complained of decreased appetite. On initial 2 admissions, the patient had mildly elevated Liver Function Tests (LFTs) see (Figure 1) and a positive Hepatobiliary Iminodiacetic Acid (HIDA) scan suggesting acute cholecystitis. On her second visit, she underwent an upper endoscopy which showed only severe esophagitis. She underwent work-up including Computed Tomography (CT) of the chest, abdomen, and pelvis, RUQ Ultrasound (US), HIDA and Magnetic Resonance Cholangiopancreatography (MRCP) showing findings consistent with chronic cholecystitis. MRCP also showed evidence of chronic hepatocellular disease or cirrhosis with nodular regeneration or infiltrative processes such as metastasis; there were no obvious metastases on the liver at this time. Due to the patient's extensive history of abdominal surgeries for hernia and her preference, non-operative management of the cholecystitis was pursued on the first two admissions.

Less than a month from her initial presentation in 8/2020, the patient presented to the ED for the third time with worsening abdominal pain and heaviness in the RUQ and anorexia. Her total serum bilirubin (Tb) was 6.3 at this time and she was visibly jaundiced. She had mild tenderness to palpation throughout the abdomen, with a positive Murphy's sign. She underwent Endoscopic Retrograde Cholangiopancreatography (ERCP) with stent placement to investigate the cause of obstructive jaundice, but no obstruction was found. At this time, she was found to have new esophageal varices and changes of portal hypertensive gastropathy in the stomach. Tb and Alkaline Phosphatase (ALP) remained elevated post ERCP. See (Figure 1) Repeat CT abdomen and pelvis without contrast showed heterogeneous enhancement patterns of the liver, highly concerning for underlying infiltrative metastasis of the liver. This was not noted on the first admission CT. See (Figure 2) it also showed a 1.3 x1.6 cm soft tissue nodule in the left chest wall, suspicious for tumor recurrence, which was confirmed on physical exam.

Visit	Total Bilirubin	ALP	AST/ALT
1st Admission	1.1	540	179/94
2nd Admission	1.8	529	137/55
3rd Admission	6.3	869	256/54
Post -cholecystectomy	8.3	769	219/66

Figure 1: Laboratory

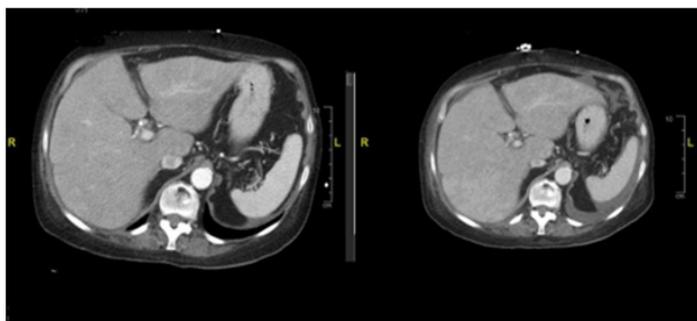


Figure 2: CT images

After multiple failed attempts at conservative management and rising Tb and LFTs and persistent RUQ pain, laparoscopic cholecystectomy was performed. Due to the suspicious findings of gastric varices and abnormal gross appearance of the liver parenchyma during laparoscopic subtotal cholecystectomy, liver biopsy was performed during the operation.

Post cholecystectomy, Tb continued to rise. See (Figure 1) MRCP was performed to rule out intraoperative damage to the biliary tree but no bile leak was found. Pathology was obtained one week after the operation, showing metastatic ER+, PR-, HER2+ breast cancer to the GB and liver. The immunoprofile was consistent with metastatic carcinoma of breast origin. It also showed chronic cholecystitis see (Figure 3, 4, 5).

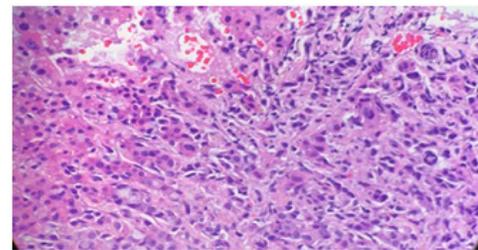


Figure 3: Metastatic carcinoma consistent with breast origin. ER+, PR-, HER2+

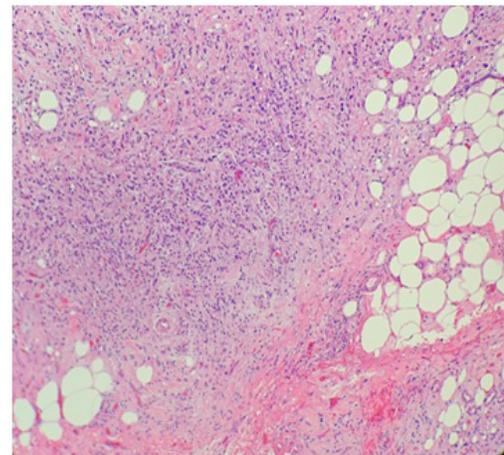


Figure 4: Extensive involvement of metastatic carcinoma consistent with breast origin

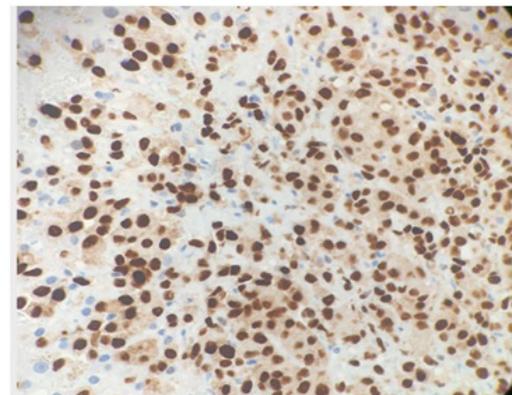


Figure 5: Intracellular staining of ER receptor

- ER (95%; 3+)
- PR is negative (<1%; 2+)

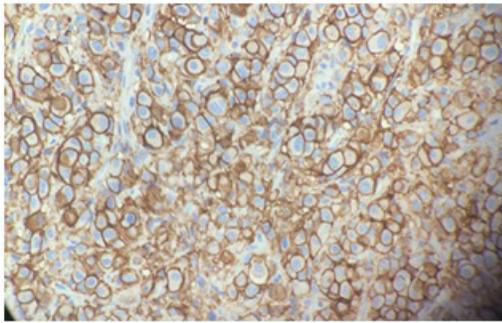


Figure 6: Positive results in tumor cells with markers CK7 and GATA-3. GCDFP-15 focally positive.

- EGFR2 staining
- Her 2 (3+)

Hematology and Oncology was consulted and recommended starting treatment with anastrozole and herceptin. The patient was discharged to a skilled nursing facility as upon discharge she continued having difficulty eating and was not strong enough to ambulate or stand independently. Arrangements were made for her to follow up with hematology oncology to receive treatments; however, about a month after the operation, she elected to switch to hospice and comfort care.

CT abdomen and pelvis without contrast showed heterogeneous enhancement pattern of the liver, highly concerning for underlying infiltrative metastasis of the liver (right), rapidly progressing since prior admission (left) when there was no discrete metastatic process

Sections of the liver show ill-defined nodules of tumor similar to that seen in the gallbladder.

GB wall was 0.4 cm thick. Sections of the GB showed extensive infiltration of the nose and the muscular wall by a subtle infiltrate of tumor cells. There is a prominent lympho vascular invasion. The adherent adipose tissue also contains tumor. Positive results in tumor cells with markers CK7 and GATA-3. GCDFP-15 focally positive.

4. Discussion

Metastasis to the GB is very rare and most of the data is obtained from case reports. In these case reports, patients present with symptoms and physical exam consistent with acute or chronic cholecystitis and undergo laparoscopic or open cholecystectomy. They are subsequently found to have metastatic disease in the GB on pathology [8]. The significance of this case report is to provide a description of the clinical presentation of metastatic disease to the GB and liver. This rare diagnosis requires a high index of suspicion and should be considered when evaluating patients with a history of malignancy, presenting with symptoms of cholecystitis along with nonspecific symptoms such as anorexia and loss of appetite. In our case, the patient had simultaneous symptoms of chronic cholecystitis and rapidly worsening obstructive jaundice due to her concurrent GB and liver metastases. Metastasis to

the liver are usually asymptomatic, but rarely can present as acute hepatic failure in 0.44% in a large retrospective study [13]. These rare cases were caused by hematologic malignancies, small-cell lung cancer and breast cancer [14, 15]. Most breast cancer metastases to the liver present as easily identifiable discrete masses on imaging. Rarely, breast cancer metastatic to the liver can have an infiltrating pattern which is less likely to be identified as metastasis on imaging. [13]. These infiltrating metastases can present as acute liver failure with anorexia, nausea, fatigue, jaundice, elevated bilirubin, ALP, low platelet count, elevated INR and sequelae of portal hypertension [15].

This case also highlights the importance of patient follow-up in outcomes of metastatic breast cancer. In this case, the patient was unable to complete both her prescribed chemotherapy and radiotherapy, both of which improve 5-year survival rate. This was caused initially by patient refusal due to side effects and later by the known effect of the COVID-19 pandemic in reducing regular outpatient follow-up. In a retrospective study of patients with breast cancer, patients with HR+/Her2+ breast cancer have a 5 year survival rate of 50.8% vs 26.5% in HR+/Her2 negative breast cancer ($p < 0.0001$) with a hazard ratio of 0.659 [7]. The increased overall survival rate is due to targeted treatment with trastuzumab which our patient did not complete [16]. Radiation therapy could also have prevented local recurrence, as the patient was noted to have 1.3x1.6 cm soft tissue nodule in the left chest on imaging during current admission. In a retrospective review of patients with non-metastatic IBC, radiotherapy improved overall 5-year survival, improving it from 40% to 55% with a p value less than 0.001 [17]. Targeted chemotherapy and radiotherapy might have slowed or prevented the spread of disease in this patient, not to mention closer follow-up which was unfortunately hindered by the COVID-19 pandemic.

5. Conclusion

Breast cancer metastatic to the gallbladder is a rare and infrequently recorded occurrence with less than 30 case reports found. In addition, it is commonly silent and rarely presents as acute cholecystitis. This case highlights an uncommon etiology of a high incidence disease and presents a diagnostic challenge. It is important to consider metastatic liver and gallbladder disease in patients with a history of prior malignancy presenting with hyperbilirubinemia, elevated liver enzymes, and symptoms consistent with acute cholecystitis. It also underlines the importance of adhering to hormonal, radiation and anti-Her2 therapy in breast cancer. The symptoms associated with this presentation are common, and there is no way to distinguish the common acute cholecystitis from the extremely rare gallbladder metastasis without resection. This patient had an even rarer concomitant presentation of gallbladder metastasis with liver metastasis, complicating the clinical picture until resection could be performed.

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