ABSTRACT

Cholangiocarcinoma (CCA) is a rare cancer of the bile duct epithelial cells and it commonly spreads to the regional lymph nodes, liver, and lungs. Bone metastasis has been reported in patients with CCA, involving both the axial and appendicular skeleton. Herein, we report a case of extrahepatic CCA with extensive bone metastases involving the calvarium, sternum, bilateral ribs and scapulae, entire spine, pelvis, and bilateral femur. To our knowledge, this is the first case report on sternum metastasis in CCA. The case presentation and review of literature highlighted the rarity of this metastasis, and health-care providers should be aware of the rare presentation of CCA.

Key Words: Cholangiocarcinoma, neoplasm metastasis, sternum

INTRODUCTION

Cholangiocarcinoma (CCA) is classified into three types according to its anatomical location along the biliary tree: intrahepatic, perihilar, or distal extrahepatic CCA. Patients with intrahepatic CCA, due to their often-late presentation, are more likely to present with nonspecific symptoms such as fever, weight loss, and/or abdominal pain. In contrast, patients with extrahepatic CCA tend to present early as they usually become symptomatic when the tumor obstructs the biliary drainage system leading to jaundice, pruritus, clay-colored stools, and dark urine. The prognosis of this malignancy is poor due to its silent clinical character, difficulties in early diagnosis, and limited therapeutic approaches; median survival (MS) is less than 24 months.

CASE REPORT

A 60-year-old female with a past medical history of hypertension presented to the emergency department with intermittent cramping lower abdominal pain, back pain, dark-colored urine, and fever for 2-week duration. The patient denied any recurring chest pain, shortness of breath, nausea, vomiting, change in bowel movement, weight loss, loss of appetite, night sweats, yellowing of the skins/eyes, or black tarry stool. The patient is a chronic smoker. Family history is significant for an unknown cancer in her mother, breast cancer in her grandmother, and lung cancer in her uncle.

Initial vital signs were as follows: blood pressure of 140/80 mmHg, pulse was in the 60 s bpm, respiratory rate of 15 bpm with oxygen saturation 99% on room air, and temperature of 98.2°F. Physical examination was unremarkable. Laboratory workup showed elevated
liver enzymes with aspartate aminotransferase of 524 U/L (normal range: 10–36 U/L), alanine aminotransferase of 640 U/L (6–29 U/L), alkaline phosphatase of >2330 U/L (33–130 U/L), gamma-glutamyl transferase of 2201 U/L (3–70 U/L), total bilirubin mildly elevated at 1.4 mg/dL (0.2–1.2 mg/dL), albumin of 3.5 mg/dL (3.6–5.1 mg/dL), prothrombin time of 16 s (10.4–12.7 s), and international normalized ratio of 1.4 (0.9–1.1). Hemoglobin and hematocrit were normal with hemoglobin of 12.2 g/dL (12–15.5 g/dL) and hematocrit of 36.4 (34.9%–44.5%). Otherwise, electrolytes were within the normal limits. Blood urea nitrogen and creatinine were normal, and the patient’s lactate dehydrogenase was 149 U/L (122–222 U/L), and lipase was 6651 U/L (73–393 U/L). The patient underwent a computed tomography scan of the abdomen which showed obstruction of the common hepatic duct proximal to the pancreas and widespread sclerotic bony metastases [Figures 1-3]. Subsequent Magnetic resonance cholangiopancreatography (MRCP) showed a 3-cm long stricture involving the mid common bile duct region close to the insertion of the cystic duct with no associated mass or regional lymphadenopathy appreciated. At that point, serum markers were ordered and showed elevated serum carcinoembryonic antigen (CEA) of 680 ng/mL (0–3 ng/mL) and elevated carbohydrate antigen 19-9 (CA19-9) of 492 U/mL (0–34 U/mL). Bone scan revealed extensive diffuse-increased activity over multiple focal areas within the calvarium as well as diffuse-increased activity in the region of sternum, bilateral ribs, scapulae, entire spine, pelvis, and femurs [Figure 4].

The patient had endoscopic ultrasound with a brush biopsy of the bile duct stricture. However, the tissue was insufficient for diagnosis. Subsequently, iliac crest bone biopsy was done which showed metastatic adenocarcinoma with immunohistochemistry staining positive for pan-keratin, CK7, CK20, MOC31, CK19, and CA19-9 most compatible with biliary origin. With the clinical, pathology, and laboratory evaluation, metastatic extrahepatic CCA was diagnosed, and the patient was started on palliative cisplatin and gemcitabine as an outpatient. The patient’s quality of life was affected, and the prognosis was poor. The most striking feature of this case is the extensive bony metastasis which includes metastasis to the sternum. To our knowledge, this is the first case of sternum metastasis from extrahepatic CCA.

DISCUSSION

The skeleton is the third most common site for metastatic disease to occur in the body overall, with only the lungs and liver with higher incidences. Within the skeletal system, the spine is the most common site of metastases. Moreover, the thoracic spine is most prone to metastatic disease as it contains the greatest volume of bone marrow per vertebrae.[4] Metastasis to the sternum is a rare event that has not been discussed thoroughly in literature; Urovitz et al. concluded that metastatic diseases are more commonly to invade the body of the sternum; they also identified that breast cancer, lymphoma, and myeloma are the most common primary lesions as opposed to Kinsella et al., who reported that the manubrium was at higher risk with the thyroid, renal, and breast carcinomas as the most common primary cancers.[5,6]

CCA is an epithelial cell malignancy arising from varying locations within the biliary tree showing markers of cholangiocyte differentiation. CCA typically advances locally to lymph nodes and metastasizes to the liver, peritoneum, lungs, and the axial skeleton, which is much more frequent than the appendicular skeleton.[7] We did an extensive literature review on CCA with bone metastasis. We searched PubMed, Google Scholar, and LILACS for this literature review using search terms “cholangiocarcinoma and bone metastasis.” All the case reports and major case studies on CCA with bone metastasis so far were reviewed. We abstracted all the relevant data from these studies with rare bone metastasis from CCA and summarized these...
in Table 1. After reviewing all the data, we concluded that sternal metastasis from CCA is a rare event and, to our knowledge, has never been reported in literature. Herein, we report the first case of sternum metastasis from extrahepatic CCA which can be added to the other rare presentations of CCA with metastasis to the bones that were reported in the literature; Harding-Kaba et al. reported a case of CCA patient with painful lower jaw swelling that was later proved to be a metastatic lesion from the CCA.[8] In addition, Wang et al. reported a case of a patient with osteolytic bone lesion in the left hip; later on, the patient was found to have hepatic CCA and thyroid carcinoma; however, a bone biopsy from the left acetabulum revealed that the metastatic lesion was of CCA origin.[9] Moreover, Jain et al. reported a case of a young woman who presented with rib that was confirmed with biopsy and immunocytochemical staining to be CCA.[10] Furthermore, Karam et al. reported a middle-aged man who presented with a liver mass and painful swelling in the ring finger that upon amputation and biopsy was diagnosed with metastatic CCA.[11]

Risk factors for bone metastasis in patients with CCA include the presence of lymph node metastasis, elevated serum CEA (≥5 ng/mL), elevated CA19-9 (≥39 U/mL), low serum albumin (<3.5 g/L), and neurological involvement with Frankel scale of A to C.[19,20] Treatment options for advanced biliary tract cancers include systemic therapy, which includes gemcitabine/fluoropyrimidine-based chemotherapy or immunootherapy (pembrolizumab) or enrollment in clinical trial. On the other hand, the treatment options for spinal metastasis in CCA patients are palliative surgery, radiation, or chemotherapy. If metastasis only limited to a single long bone, orthopedic consultation may play a role.

The prognosis for CCA with bony metastasis is poor. Sangsin et al. in a study of 182 patients with CCA presented with spinal metastasis showed an overall MS of 88 days with a survival rate of 10% after 1 year.[20] The MS varies depending on the treatment of the primary CCA as the highest MS was seen in percutaneous biliary drainage with 149 days, then tumor resection with 112 days, and the least was palliative treatment with 65 days only.[20] CCA patients with spinal metastasis who underwent palliative spinal surgery had an MS of 136 days, whereas patients who had radiotherapy alone had an MS of 112 days, and those who received palliative treatment only had an MS of 102 days.[20] Thus, the treatment

| First author  | Age | Sex  | Year | Metastatic side                             | References |
|---------------|-----|------|------|---------------------------------------------|------------|
| Harding-Kaba  | 64  | Female | 2008 | Mandible                                   | [8]        |
| Wang          | 58  | Female | 2015 | Acetabulum                                  | [9]        |
| Jain          | N/A | Female | 2004 | Ribs                                       | [10]       |
| Karam         | N/A | Male   | 2017 | Ring finger                                | [11]       |
| Carisle       | 60  | Female | 1999 | Humerus                                    | [12]       |
| Miyamoto      | 67  | Female | 2007 | Left occipital bone                        | [13]       |
| Lahrach       | 58  | Female | 2010 | Humerus                                    | [14]       |
| Federico      | 71  | Male   | 2013 | Humerus                                    | [15]       |
| Karanja       | 75  | Female | 2013 | Fibula                                     | [16]       |
| Fujimoto      | 64  | Female | 2013 | Left orbit and right parietal bone         | [17]       |
| Fujimoto      | 64  | Female | 2013 | Left orbit, left parietal bone, and left temporal bone | [17] |
| Fujimoto      | 64  | Female | 2013 | Right petrous bone and right occipital bone | [17] |
| MacKenzie     | 61  | Female | 2017 | Femur                                      | [18]       |
plan for each patient should be evaluated carefully and correlated with patient’s clinical status. Moreover, all the recommendations reported are for solitary sternal metastasis. However, since diffuse bone metastasis, in general, has a poorer prognosis and the sternum is an uncommon site for bony metastasis, we propose that sternal involvement in patients with metastatic CCA carries a poor prognosis. Eventually, our patient was treated with systemic therapy and pain control as part of palliative treatment.

CONCLUSION

Metastatic CCA to the bone is extremely rare. Metastasis to the sternum is even rarer, and to our knowledge, this is the first case reported on sternum metastasis and one of the two case reports of CCA presenting with simultaneous involvement of both axial and appendicular skeleton. Health-care providers should be aware of the rare presentation of CCA and should always consider this as a differential diagnosis in CCA patients who present with bone pain. Since the prognosis is extremely poor, pain management in addition to conventional chemotherapy is the mainstay of treatment to improve the quality of life of the patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Research quality and ethics statement

We declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network CARE case report guidelines.

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