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An Unusual Presentation of Advanced Intrahepatic Cholangiocarcinoma: When Biopsy Results Fail

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Female, 67
Final Diagnosis: Intrahepatic cholangiocarcinoma
Symptoms: Atypical chest pain
Medication: —
Clinical Procedure: Liver biopsy
Specialty: Internal Medicine/Oncology

Objective: Rare disease
Background: Intrahepatic cholangiocarcinoma is a rare condition which typically occurs in males between 50 and 70 years of age, and presents with symptoms related to biliary obstruction including jaundice, pruritus, and dark urine. Other common symptoms at presentation include abdominal pain, weight loss, and fever.
Case Report: We present a case of a 67-year-old female initially presenting with chest pain at rest, found to have a lung nodule on diagnostic imaging at the time of admission. On further imaging, a 9 cm liver lesion was incidentally discovered, initially suspicious for hepatocellular carcinoma on imaging, with initial biopsy staining CK7 positive, and CK20 negative. The patient also had an elevated alpha-fetoprotein level. Biopsy results were later confirmed as moderately differentiated adenocarcinoma consistent with intrahepatic cholangiocarcinoma.
Conclusions: This report illustrates an unusual presentation of intrahepatic cholangiocarcinoma. Although rare, cholangiocarcinoma is diagnosed most frequently as an incidental finding on imaging studies. With quick work-up and successful biopsy results, patients can undergo surgical or chemo-radiation therapy earlier, potentially leading to a longer survival time.

MeSH Keywords: Carcinoma, Hepatocellular • Chest Pain • Cholangiocarcinoma • Solitary Pulmonary Nodule

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/906165>

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Background

Intrahepatic tumors have traditionally been classified as primary liver cancers. The term cholangiocarcinoma has recently been used to describe bile duct cancers within the intrahepatic, perihilar, and distal (extrahepatic) biliary tree. The tumors typically originate either within the small intrahepatic ductules or larger intrahepatic ducts proximal to the bifurcation of the left/right hepatic ducts [1].

Classically, patients with advanced disease will present with symptoms including jaundice, pruritus, clay-colored stools, and dark urine [1]. Multiple risk factors have been associated with the development of cholangiocarcinoma, including primary sclerosing cholangitis, congenital hepatic fibrosis, choledochal cysts, liver fluke infections, cholelithiasis, hepatolithiasis, Thorotrast contrast dye exposure, viral hepatitis, other chronic liver diseases, obesity, and HIV infection [2].

While the molecular pathogenesis remains unclear, it is suspected that conversion from normal to malignant bile epithelium generally requires a stepwise accumulation of genetic abnormalities. Molecular defects involving several oncogenes and tumor suppressor genes have been studied and seem to be related to more aggressive tumor phenotypes [3].

Case Report

A 67-year-old Caucasian female presented with complaints of atypical chest pain, described as a sensation of nausea, with bilateral superior chest/low anterior cervical pressure and paresthesia. She developed a posterior throbbing headache while she was sitting on her couch to rest. These symptoms relapsed every five to 10 minutes over several hours; then occurred on several isolated occasions over the next three to four days until the time of admission. She also mentioned several episodes of bilious emesis during her first occurrence. At the time of presentation, she denied overt chest pain, hemoptysis, fever, chills, shortness of breath, diarrhea or constipation, or urinary symptoms.

Past medical/surgical history included COPD of unspecified severity with no home oxygen requirement, hypothyroidism, hypertension, GERD, depression, diabetes mellitus type 2, diastolic congestive heart failure, remote fall history with right intertrochanteric fracture, and history of a cholecystectomy performed three years prior, hysterectomy, thyroidectomy, and right total knee replacement. Social history included former tobacco abuse, quit date three years prior, with 72 pack year history. She denied current or former recreational drug or alcohol use. Family history included mother with fatal course of bronchitis, a father with history of metastatic melanoma at age 70 years, and a brother with history of a myocardial infarction.

Figure 1. Axial CT image of the pulmonary nodule, felt to represent a granuloma in the left upper lobe.

On admission, the patient's initial vitals included blood pressure 130/78 mm Hg, pulse 80, respirations 20, temperature 97.9°F (36.6°C), and an oxygen saturation of 97% on room air. Physical examination revealed a well-developed, obese, alert and oriented female in no acute distress, sitting up in bed. Dermatologic examination revealed multiple healed surgical scars present over abdomen and right knee. Head, ears, eyes, nose, throat (HEENT)/ neck/ cardiovascular/ respiratory/ gastrointestinal/ musculoskeletal/ neurological/ and immunological examinations were all grossly unremarkable. Initial ECG was unremarkable for acute ischemic changes.

Laboratory assessments on admission were as follows: white blood cell count (WBC) 12.3; hemoglobin/hematocrit (Hgb/Hct) 14.0/44.0; platelets 219; sodium 142; potassium 4.8; chloride 104; carbon dioxide 23; blood urea nitrogen (BUN) 25; creatinine 1.00; calcium 10.2; troponin <0.012; CKMB 0.47; CPK 75; INR 0.85; prothrombin time 9.9; partial thromboplastin time 30.4; and hemoglobin A1c 5.8%.

The patient was admitted to a telemetry floor as an acute coronary syndrome rule out. Serial ECG's and cardiac enzymes were unremarkable for an acute ischemic cardiac process. A single anterior-posterior view chest x-ray showed presence of emphysema and a possible small left upper lobe lung nodule.

Further imaging of the patient's chest with CT imaging utilizing IV contrast revealed mild emphysema and a 9 mm lobulated nodule in the left upper lobe (Figure 1), which was considered likely to represent a granuloma. Evidence of prior granulomatous disease with probable focal scarring in both lower lobes was observed, and several small punctate nodular densities were

Figure 2. (A, B) These images show the 9.4×9.8 cm right hepatic lobe mass on axial and coronal views; (B) 3 cm heterogeneous kidney mass (yellow arrow).

noted laterally in the right mid lung field. Lastly, a large, nearly 10 cm heterogeneous low density mass posteriorly in the right hepatic lobe, noted to be new since a November 2013 study, and considered concerning for neoplasm was noted, with no notable chest lymphadenopathy, pneumothorax, or pleural effusion.

A CT scan of the abdomen/pelvis with and without IV contrast was then obtained the following day, showing the presence of a large, heterogeneous, centrally necrotic irregular mass in the posterior segment of the right lobe of the liver superiorly measuring approximately 7.5×9.8×8.5 cm (Figure 2A), which demonstrated irregular discontinuous peripheral enhancement, thought to be highly suggestive of primary hepatocellular carcinoma. A 3 cm heterogeneous irregular mass was also noted in the medial aspect of the right kidney demonstrating mild continuous enhancement, concerning for primary renal cell carcinoma (Figure 2B). No evidence of bowel obstruction, acute inflammatory process, or adenopathy was seen within the abdomen or pelvis. Lastly, a tiny left renal cyst was observed.

It is important to mention the patient's prior cholecystectomy was performed at an outside institution and information surrounding the surgery was unavailable. However, a CT abdomen/pelvis without contrast was obtained several months after the surgery, though still three years prior to this admission, due to an episode of right flank pain. This imaging modality showed presence of mild hepatic steatosis with an absent gallbladder. Additionally, the 3 cm mass over the right kidney was present on this study and appeared to have been unchanged from prior study. This lesion hence forward was considered benign.

At this time, an alpha-fetoprotein (AFP) level was obtained and determined to be 15.7. A CT-guided core biopsy was also obtained of the right hepatic lesion, specifically four 18-gauge samples were obtained, two from the central portion of the mass and two from the anterior periphery. It revealed the presence of poorly differentiated adenocarcinoma, with immunohistochemical staining showing malignant glands positive for CK7, while negative for CK20 and CDX2. The patient at this time was discharged from the hospital with close follow-up scheduled with the oncology office for further work-up.

Outcome and follow-up

The patient had a PET scan with CT fusion approximately one week after discharge showing nonspecific activity over the small left upper lobe nodule with a standardized activity unit (SUV) of 1.7, with hypermetabolic activity (SUV 11.5) seen over the right hepatic mass. The kidneys and adrenal glands were reportedly unremarkable. The differential at this point was considered broad by the oncology service, and included neoplasms of bile duct, breast, and lung origins.

The patient required an additional CT-guided liver biopsy procedure, where six more 18-gauge core samples were obtained (Figure 3). These were obtained two weeks after discharge, and were sent for tissue of origin testing at an outside facility, utilizing micro RNA testing. The results suggested the presence of moderately differentiated adenocarcinoma consistent with cholangiocarcinoma.

Later, a CT-guided biopsy of the patient's left lung lesion was consistent with metastatic cholangiocarcinoma. The patient was then started on chemotherapy with gemcitabine and oxaliplatin. The patient tolerated only a few cycles of chemotherapy before readmission several months later for hepatic encephalopathy and septic shock, which the patient would die from during the hospital stay.

Discussion

The patient, after the repeat hepatic biopsy results, was formally diagnosed with primary intrahepatic cholangiocarcinoma. Roughly 5% to 10% of cholangiocarcinomas are of the intrahepatic subtype, and they typically originate from small intrahepatic ductules or large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts [4]. Tumors occurring at the confluence of the left and right hepatic ducts represent Klatskin tumors [5]. Less than 10% of cases documented are found to represent intrahepatic disease [6]. Over the last several decades, the incidence of intrahepatic cholangiocarcinoma has increased internationally. However, the increased incidence is not correlated to an increase in earlier staged lesions [7,8].

Cholangiocarcinoma can be divided into three subtypes: sclerosing, nodular, and papillary [9]. Sclerosing tumors are noted to be by far the most common, causing a rather significant desmoplastic reaction, with extensive fibrosis. The pathology report of our patient's tumor commented specifically on the large amount of necrotic and fibrotic changes, making this the most likely subtype.

Common signs and symptoms include jaundice, pruritus, clay-colored stools, and dark urine when the tumor invasion leads to biliary system obstruction. The intrahepatic subtype can also result in complaints of abdominal pain, weight loss, fever, malaise, fatigue, and night sweats. However, some patients remain asymptomatic, with lesions seen incidentally on screening imaging for abnormal liver function tests, or in known hepatitis B or C patients [10]. The patient in our case possessed none of the described symptoms; however, she did mention a non-specific chest pressure and paresthesia sensation. The initial presentation was misleading due to the absence of common symptoms associated with intrahepatic malignancy, especially since the patient's chest pain symptoms improved during her hospital stay. This made the need for a confirmatory tissue diagnosis paramount to facilitate appropriate care.

There are several risk factors for cholangiocarcinoma, including primary sclerosing cholangitis (PSC) and fibropolycystic liver disease [11]. Chronic liver diseases, including liver cirrhosis and hepatitis, have also been correlated with cholangiocarcinoma,

Figure 3. Hematoxylin and eosin stained slide of the repeated liver biopsy at approximately 400× magnification. Malignant cells are seen surrounding the biliary ductules (red arrows).

specifically of the intrahepatic subtype. We felt that this patient did not possess these conditions, given the absence of alcohol and drug use history, the original CT abdomen/pelvis study showing no presence of cirrhotic changes, and follow-up laboratory studies showing normal liver function tests. Additionally a check for hepatitis B surface antigen after discharge was negative.

The patient was noted to have a slightly elevated AFP level, which led to the consideration of primary hepatocellular carcinoma, especially given the initial radiology impression strongly in favor of a primary hepatocellular carcinoma lesion. This was also taken into consideration with the patient's initial biopsy results staining positive for CK7 but negative for CK20, which is nonspecific for primary hepatocellular carcinoma or cholangiocarcinoma. Given these characteristics of the liver lesion, there was suspicion for hepatocellular carcinoma. However, after obtaining the initial pathology report showing the presence of poorly differentiated adenocarcinoma, the accuracy of the results was in question.

It was also unclear where the site of origin laid, whether in the bile ducts, breasts, or the lungs being the primary sites of concern. After discussion with the pathologists, the recommendation to obtain slides for micro RNA testing was made, although this implied additional tissue was needed, so the patient was scheduled for another hepatic biopsy. Despite the presence of some necrosis on the initial samples, this was considered minimal by the pathologists report and did not significantly alter the results. Additionally, the sample sizes ranged from 1.0 cm to 1.8 cm, which were considered large enough for accurate interpretation.

There was also some discussion over the possibility of an underlying combined hepatocellular-cholangiocarcinoma. Combined

hepatocellular-cholangiocarcinoma is known as a recently acknowledged distinct subtype of cholangiocarcinoma, seen in patients with elements of both cholangiocarcinoma and hepatocellular carcinoma [2]. For our patient, further laboratory work was obtained after discharge, including a normal hepatitis B surface antigen, with normal liver function tests and total bilirubin. In conjunction with the aforementioned biopsy results, this diagnosis was excluded. Primary colon cancer was ruled out initially from the first CT diagnostic imaging performed, in addition to the PET scan results.

It was important to differentiate between hepatocellular carcinoma and cholangiocarcinoma. Although both malignancies can be treated curatively with hepatic resection, liver transplant, or chemoembolization, advanced disease therapies differ more significantly. Advanced hepatocellular carcinoma has been treated with doxorubicin as single drug therapy, but has shown inefficacy with a response rate of about 15% to 20% [12]. Multiple other agents, such as cisplatin, 5-fluorouracil, etoposide, and combinations thereof, have demonstrated either similar or lower efficacy. The tyrosine kinase inhibitor sorafenib has been developed recently, though it has shown only an improved survival of three months [13]. These modalities were considered as the final diagnosis was being made.

Once the final diagnosis was determined, multiple combinations of agents were considered for this patient's chemotherapy. The first choice therapy considered was the combination of gemcitabine and cisplatin, which has been shown to provide a median survival of approximately 9.30 months [14], and 11.7 months [15], with palliative care having a survival timeframe averaging six months, with a five-year survival rate around 1.2% [16]. However, the patient was noted at the time of her office visit to have a slightly elevated serum creatinine of 1.40, and was not considered a candidate for this drug regimen. Instead, the patient was started on a non-cisplatin regimen, including oxaliplatin with gemcitabine which has also been shown to have a median survival of 11 months in unresectable biliary tract cancers [17].

Regretfully, there was little discussion regarding the role of chemotherapy versus palliative care during this patient's initial hospital visit. In retrospect, this patient survived about nine months from time of diagnosis with 10 cycles of oxaliplatin with gemcitabine administered over a five-month period. Though this patient initially tolerated the chemotherapy regimen, she became increasingly weak, eventually developing an altered mental state leading to a hospital admission, where she would die as a result of her disease. It is difficult to state whether being exposed to the effects of chemotherapy was a more desirable outcome for this patient. Palliative care could have been offered to determine if the goals of care the patient desired were different than what the chemotherapy regimen

offered. Also, palliation could have optimized the quality of life the patient had until death. Every treatment option, including palliative therapy alone, should be offered and explained to patients who are diagnosed with an advanced stage malignancy.

Conclusions

The presented case demonstrates several important aspects of intrahepatic cholangiocarcinoma. First, several patients can present without symptoms or abnormal liver functions tests, relying heavily on incidental imaging findings to initiate work-up. Second, radiology findings and tumor markers must be correlated with pathology findings for a final diagnosis, especially in cases where a general consensus for a specific diagnosis does not exist. Our patient showed a unique presentation since in the setting of an elevated AFP, the radiologist's findings correlating with hepatocellular carcinoma, and the initial biopsy samples staining positive for CK7 but negative for CK20; our patient was ultimately diagnosed with cholangiocarcinoma.

The final diagnosis required a second CT-guided hepatic biopsy for confirmation, which occurred after discharge and required two additional weeks. Only after the second biopsy sample confirmed the diagnosis of moderately-differentiated cholangiocarcinoma, did the attending oncologist recommend that the patient be evaluated by a surgeon for potential hepatic resection. It was decided that the patient would not be a candidate for such a procedure, and the patient was sent for a biopsy of the left upper lobe lesion in order to determine the stage of the malignancy.

Additionally, the patient required a biopsy of the left lung lesion to be scheduled at an outside facility, which required more time to contribute to the final diagnosis and complete tumor staging. This procedure could only be done at an outside tertiary care facility, since interventional radiology was not an available subspecialty offered at the institution where primary work-up had occurred. This delay prevented the patient from undergoing chemotherapy at an earlier time, which could have potentially led to an increased survival time.

Most cases of cholangiocarcinoma are extrahepatic in nature, and present most commonly with abnormal laboratory findings. The aforementioned case describes an intrahepatic subtype, with complicating components suggesting a possible hepatocellular carcinoma. This patient required multiple hepatic biopsies to confirm a final diagnosis, resulting in an increased hospital stay, a higher financial burden, and a delay in treatment. Clinicians should be made more aware of the misleading nature of intrahepatic cholangiocarcinoma to improve the efficiency of obtaining an accurate, final diagnosis. Retrospectively, further evaluation for hepatitis B and C, in addition to utilizing

more samples from the first CT-guided liver biopsy during the initial hospital stay should have been conducted to determine the underlying diagnosis at a faster pace.

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Conflict of Interests

None.

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