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Case Report

Pure squamous cell carcinoma of the gallbladder in a patient with perforated calculus cholecystitis

Alice V. Nicol[1,2]*, Jessica Y. S. N.[1,3], Rachel Colbran[1,4]

[1]Department of General Surgery, Ipswich Hospital, Ipswich, Queensland, Australia
[2]University of Queensland, Brisbane, Queensland, Australia
[3]Griffith University, Gold Coast, Queensland, Australia
[4]University of Queensland, Brisbane, Queensland, Australia

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***Correspondence:**
Dr. Alice V. Nicol,
E-mail: alicevnicol@gmail.com

ABSTRACT

Gallbladder carcinoma is one of the most common and aggressive malignancies to arise from the biliary tract. However, pure squamous cell carcinoma (SCC) originating from the gallbladder is exceptionally rare, reported to represent less than 1% of all malignancies. An 89-year-old Australian male presented with symptoms and imaging consistent with acute calculus cholecystitis. After failed conservative management he underwent a subtotal cholecystectomy. Diagnosis on histopathological examination demonstrated SCC of the gallbladder. This case highlights the importance of considering gallbladder malignancy including rare histological subtypes such as SCC in patients presenting with symptoms consistent with benign gallbladder disease particularly in the elderly population.

Keywords: Gallbladder carcinoma, Squamous cell carcinoma, Gallbladder malignancy

INTRODUCTION

Gallbladder carcinoma is one of the most aggressive malignancies to arise from the biliary tract and carries an incidence in the United States of 1.2 per 100,000 with the majority of diagnoses occurring in advanced stages.[1-3] Gallbladder malignancy is incidentally found in 0.19 to 3.3% of patients undergoing surgical procedures for presumed benign biliary disease.[1,2,4] Pure squamous cell carcinoma is even rarer and represents less than 1% of all gallbladder malignancies – as opposed to adenocarcinoma which accounts for up to 90%.[1-3] Given that the incidence of malignancy increases with age, it is important to consider gallbladder malignancy as a differential diagnosis in elderly patients presenting with both calculus or acalculous cholecystitis. Currently the only curative treatment is surgical resection.[3] Often, this subset of the population is medically comorbid and not ideally suited for repeated surgical exploration. Thus, a high index of suspicion during initial surgical intervention should be maintained so as to attempt an extended cholecystectomy with oncological margins to allow for greatest chance of complete resection at the initial operation.

CASE REPORT

An 89-year-old Australian male presented to the emergency department with an 8-day history of worsening generalised abdominal pain and associated fevers up to 38.7 degrees Celsius.

On arrival he was tachycardic (heart rate 121 beats per minute) but all other vital signs were within normal limits. Examination revealed mild jaundice with scleral icterus, bilateral poor air entry at the bases on auscultation, and a soft but generally tender abdomen with greatest tenderness in the right upper quadrant on abdominal exam. Murphy's sign was equivocal. There was no evidence of gross peritonitis.

His past medical history was significant for atrial fibrillation for which he had taken apixaban the morning of presentation, chronic obstructive pulmonary disease with a baseline exercise tolerance of 80 meters, gout, chronic kidney disease with a baseline creatinine of 200 umol/l, hypertension and cervical spondylosis. He had no previous abdominal surgery. He had no history of travel, no known gallbladder polyps or stones, and no history of pancreaticobiliary disease.

Initial laboratory evaluation demonstrated the following: creatinine of 212 umol/l (40-100 umol/l), mildly deranged liver function with a total bilirubin 48 umol/l (<20 umol/l), conjugated bilirubin 10 umol/l (<4 umol/l), alkaline phosphatase 97 U/l (30-110 U/l), gamma-glutamyl transferase 40 U/l (<38 U/l), alanine aminotransferase 15 U/l (<34 U/l), aspartate aminotransferase 21 U/l (<31 U/l) and lipase of 38 U/l (<60 U/l). Full blood count demonstrated a white cell count (WCC) of 14.3×10^9/l (4.0-11.0×10^9/l) and a C-reactive protein of 325 mg/l (<2 mg/l). A non-contrast computed tomography (CT) abdomen was performed given impaired renal function, which revealed a 2.3cm gallstone and an oedematous gallbladder wall suggestive of cholecystitis (Figure 1).

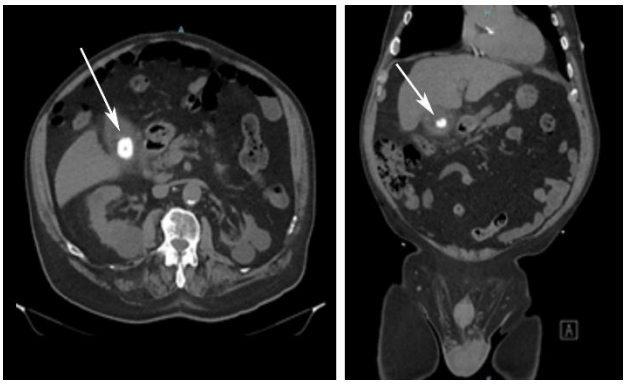

Figure 1: Axial and coronal views of the pre-operative CT scan, demonstrating a 2.3 cm gallstone (arrow) and changes consistent with cholecystitis including gallbladder wall thickening and pericholecystic fat stranding.

A decision was initially made to trial non-operative management due to the patient's significant medical comorbidities, relatively poor baseline function and active anticoagulation with apixaban. Intravenous fluid resuscitation, intravenous antibiotics (amoxicillin with clavulanic acid), analgesia, physiotherapy and mechanical venous thromboembolic prophylaxis were initiated with planned frequent clinical review by the surgical team. This patient subsequently failed conservative management. On day 4 of admission he deteriorated with worsening abdominal discomfort, tachycardia to 130 beats per minute, and new right upper quadrant localised peritonitis. He developed a type 2 myocardial infarction with mild troponin rise. A multidisciplinary decision to proceed with operative intervention was made in consultation with the cardiology and haematology teams. The patient underwent a laparoscopic subtotal cholecystectomy on day 6 of admission; intraoperative findings revealed acute cholecystitis with perforation at the Hartmann's pouch which was walled off with omentum. A large gallstone was noted to be embedded within Hartmann's pouch. The patient was admitted to the intensive care unit post procedure and had a relatively uncomplicated post-operative course with a further 3 days intravenous antibiotics required.

Histopathological examination of his operative specimen demonstrated moderately differentiated squamous cell carcinoma throughout the gallbladder wall, invading through muscle and into subserosal fat. Extensive lymphovascular invasion was demonstrated with tumour at the serosal surface. After risk stratification with anaesthetics, no further surgical resection was recommended due to his high-risk medical comorbidities and his age. Consultation with medical oncology was undertaken and further investigations to exclude distant primary site for the malignancy were undertaken including a positron emission tomography (PET) scan. PET scan 10 days after the operation failed to demonstrate fluorodeoxyglucose (FDG) uptake distant to the gallbladder fossa (Figure 2) and in light of PET results the opinion of the multidisciplinary team was the histology results represented primary gallbladder squamous cell carcinoma and was deemed unsuitable for adjuvant chemotherapy given his significant comorbidities and lack of significant survival benefit.

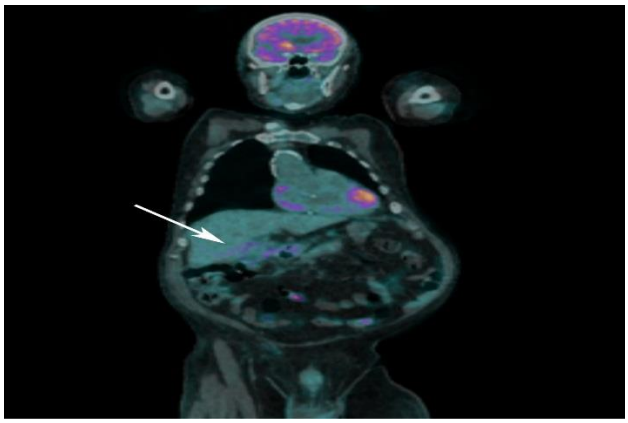

Figure 2: Positron emission tomography (PET) scan, coronal view, taken 10 days post-operatively demonstrating increased fluoro-deoxyglucose (FDG) uptake in the gallbladder fossa (arrow).

The patient was initially seen in the surgical outpatient clinic 6-weeks post discharge and was recovering well. At his five-month surgical review, CT scan showed disseminated peritoneal disease with omental caking and direct liver invasion predominantly in segment V (Figure 3). He was subsequently referred to the palliative care service. The patient currently continues care under the palliative care service and has had multiple admissions for symptom management including drainage of symptomatic

malignant ascites. He continued to function at home with his wife 12-months after diagnosis.

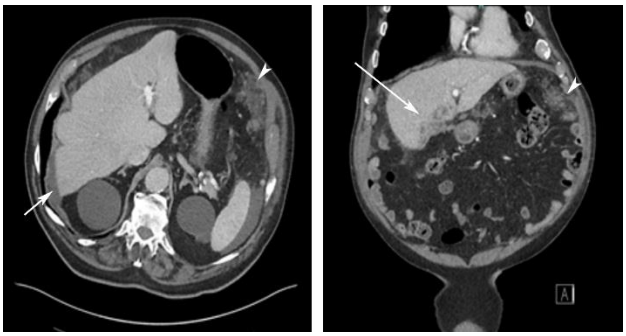

Figure 3: Axial and coronal views of a CT scan 5 months post-operatively showing direct liver invasion (long arrow), malignant ascites (short arrow) and omental caking (arrowhead) consistent with disseminated peritoneal disease.

DISCUSSION

Gallbladder carcinoma is the one of the most common and aggressive malignancies to arise from the biliary tract, with the incidence of gallbladder cancer in the United States being reported as 1.2 per 100,000 with the majority of diagnosis occurring in advanced stages.[1-3] Early diagnosis tends to result incidentally on histological diagnosis from cholecystectomies performed for symptomatic gallstone disease.[1] The incidence of malignancy on histological examination of cholecystectomy specimens performed for presumed benign biliary disease is reported in the literature between 0.19 and 3.3%, and between 47 and 80% of gallbladder malignancy is diagnosed incidentally.[1,2,4] Survival from gallbladder malignancy is poor, with approximately 90% of patients having advanced disease at diagnosis.[3] The reported five year survival is as low as less than five per cent, however prognosis is improved in patients where malignancy is incidentally diagnosed as this often results in early stage disease at diagnosis.[1] Up to 74% of patients undergoing re-exploration have evidence of residual disease and thus surgery for re-exploration and further excision has been reported to improve median survival.[2]

There are numerous histopathological types of gallbladder malignancies. The most common gallbladder malignancy is adenocarcinoma, with other malignancies including papillary adenocarcinoma, mucinous adenocarcinoma, intestinal type adenocarcinoma, clear cell adenocarcinoma, small cell carcinoma, and signet ring cell carcinoma.[2,5] Pure squamous cell carcinoma is very rare and has been reported to represent less than 1% of gallbladder malignancies.[1-3] More frequently, adenocarcinoma is seen with a degree of squamous differentiation.[2,5] Whereas gallbladder adenocarcinomas are thought to arise from the epithelial lining, it has been hypothesised that squamous cell carcinoma arises from squamous metaplasia already present in gallbladder mucosal cells or via squamous differentiation of adenocarcinoma cells.[3,6,7] Gallbladder malignancy incidence increases with increasing age and is two to six times more common in women compared men.[3] Reported risk factors for gallbladder malignancy include chronic inflammation, gallstones, polyps, and porcelain gallbladder.[3] Surgical resection is currently the only potentially curative treatment for gallbladder cancer with limited data on the role of adjuvant therapies, and only a limited number of case reports documenting poor outcomes regardless of adjuvant treatments.[3]

Preoperative diagnosis is difficult given vague symptomatology which often mimics benign gallstone disease.[4] Common symptoms and signs at presentation include right upper quadrant abdominal pain, palpable mass (Courvoisier sign), fever, jaundice, positive Murphy's sign on examination, nausea, vomiting, weight loss and thickened gallbladder wall or mass lesion on ultrasound (USS).[8] However preoperative imaging with USS and CT often show features consistent with cholecystitis and cholelithiasis.[8] Gallbladder malignancy has been hypothesised to cause cholecystitis in the absence of gallstones through obstruction of bile flow by the tumour, and the reported incidence of gallbladder malignancy presenting as acute cholecystitis is 2.3%.[9] Gallbladder SCC exhibits direct and early invasion into liver and adjacent organs including duodenum, stomach and transverse colon, however has lower incidence of lymph node metastases compared to adenocarcinomas.[2,5]

SCC of the gallbladder on histopathological examination have prominent keratinisation with keratin pearls, intercellular bridges and keratohyalin granules and often have areas of squamous metaplasia distant from malignancy.[10] Microscopic evaluation often demonstrates central deposition of keratin within infiltrative nests.[5]

CONCLUSION

In summary, although rare, pure SCC can arise from the gallbladder. The incidence of gallbladder malignancy increases with age, and therefore it should be considered as a differential diagnosis in older patients presenting with symptoms and investigations consistent with gallstone disease including calculus cholecystitis. It should also be considered as a differential for elderly patients presenting with imaging and clinical findings consistent with acalculous cholecystitis in the absence of typical risk factors given the potential for malignancy to cause cholecystitis.

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