Case Report

Metastatic melanoma of the gallbladder in a patient with acute cholecystitis: a case report and review of the literature

Emily Sawyer¹*, Kayla Tran², Lydia Kalpakos², Sujith Ratnayake¹

¹Department of General Surgery, Caboolture Hospital, Caboolture, Queensland, Australia
²Department of Anatomical Pathology, Pathology Queensland, The Prince Charles Hospital, Laboratory Group, Queensland, Australia

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*Correspondence:
Dr. Emily Sawyer,
E-mail: Emily.sawyer@health.qld.gov.au

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ABSTRACT

Melanoma is an aggressive type of cancer that has significant metastatic potential. Most commonly, distant melanoma metastases are identified in the lung, liver and brain. Metastatic melanoma of the gallbladder is extremely rare and is usually associated with widespread gastrointestinal deposits which purports a poor prognosis. Whilst an uncommon site of melanoma metastases, it accounts for 50% of all tumour metastases to the gallbladder. There are a small number of case reports and case series that describe different manifestations of melanoma metastases to the gallbladder. We report the case of a patient who presented with acute cholecystitis on a background of cholelithiasis and underwent a laparoscopic cholecystectomy with histopathology identifying gallbladder metastasis from malignant melanoma.

Keywords: Acute cholecystitis, Metastatic melanoma, Laparoscopic cholecystectomy

INTRODUCTION

Whilst rates of metastatic melanoma are increasing worldwide, metastatic deposits to the gastrointestinal tract are uncommon. In particular, metastases of melanoma to the gallbladder are scarcely reported across the literature. With only a small number of case reports and case series available, appropriate investigation and diagnosis of gallbladder metastatic melanoma is poorly understood. Gallbladder melanoma metastases are typically asymptomatic and are often discovered incidentally during surveillance imaging. However, there have been accounts of biliary colic and acute cholecystitis as a result of obstructive metastases. Appropriate management of metastatic melanoma of the gallbladder is currently unclear and the survival rate after diagnoses appears to vary significantly between cases. We report the case of a patient who presented with cholecystitis and underwent a laparoscopic cholecystectomy. It was subsequently discovered on histopathology they had melanoma metastases to the gallbladder as a first site of recurrence as a first site of recurrence four years after a primary melanoma diagnosis.

CASE REPORT

A 75-year-old female initially presented to our centre with a five-day history of epigastric pain. On examination she had epigastric and right upper quadrant tenderness with palpation but there was no rebound tenderness or palpable masses. She was haemodynamically stable and afebrile. A blood count revealed a normal white cell count of 8.600/mm², a moderate increase of gamma-glutamyl transferase, alanine aminotransferase and aspartate aminotransferase and a normal total bilirubin. Abdominal ultrasonography (USS) demonstrated a hydropic appearing gallbladder with a normal wall thickness (<3 mm), cholelithiasis with multiple gallstones...
(maximum size 44 mm) and a 21 mm non-mobile calculus in the gallbladder neck (Figure 1).

Figure 1: Ultrasound demonstrating thin-walled gallbladder and a 21 mm stone in gallbladder neck.

The patient underwent a laparoscopic cholecystectomy. Intraoperatively, there was evidence of acute necrotic cholecystitis with empyema. The distended gallbladder was initially decompressed and fluid sent for culture. An intra-operative cholangiogram (IOC) was concerning for a filling defect obstructing flow of contrast into the duodenum possibly representing choledocholithiasis. However, a subsequent MRCP did not identify any choledocholithiasis or other intrinsic or extrinsic obstruction. There were no other intra-operative or post-operative concerns.

On gross pathological examination the gallbladder measured 120 mm in length and up to 50 mm in diameter. There were multiple calculi were present within the lumen. The mucosal surface appeared hemorrhagic, with multiple scattered hemorrhagic-appearing polyps, ranging in size from 4×3×2 mm to 15×12×5 mm (Figure 2). On microscopic examination there were background changes of acute cholecystitis. The hemorrhagic-appearing polyps seen macroscopically were tumour deposits of metastatic malignant melanoma, invading into perimuscular connective tissue but not involving the free serosal surface (visceral peritoneum). The tumour deposits were comprised of diffuse solid infiltrates of pleomorphic epithelioid cells showing marked nuclear pleomorphism and cytoplasmic melanin pigment (Figure 3).

There was no lymphatic or haematological invasion and the specimen contained no lymph nodes. On immunohistochemistry the tumour cells showed positivity for melanoma markers HMB45 and MelanA and were also immunohistochemically positive for BRAF V600E mutation (Figure 4).

Figure 2: Macroscopic appearance of the gallbladder with a mucosal surface with multiple scattered hemorrhagic-appearing polyps (scale is in millimeters).

Figure 3 (A and B): Low-power and high-power photomicrograph with hematoxylin-eosin stain of a specimen from the gallbladder demonstrating malignant melanoma.
Figure 4 (A and B): Neoplastic cells positively immune-stained with BRAF V600E and HMB45 antibody.

Four years previously, the patient had undergone an excision of a melanoma on her right arm under local anaesthesia by her general practitioner. Histologically, the specimen revealed nodular malignant melanoma with a Breslow thickness of 0.9mm, invasive to Clark’s anatomic level II. The patient underwent a re-excision with subsequent histopathology demonstrating dermal scar with no residual malignancy. No sentinel lymph node biopsy was performed.

A positron emission tomography (PET) scan identified increased FDG update in the left thigh and right elbow suspicious for subcutaneous metastatic deposits and concerning features of two frontal cerebral metastases. An MRI later confirmed cerebral metastatic melanoma. The patient was therefore classified as having stage IV melanoma (T1bNxM1d, AJCC classification).1 At the time of writing, the patient is currently undergoing immunotherapy under the combined Nivolumab and Ipilimumab protocol.

**DISCUSSION**

Melanoma arises from gene mutations and tumour microenvironmental alterations of melanin-producing dendritic cells, named melanocytes.2 Whilst usually cutaneous, melanoma also has the potential to develop from visceral mucosa likely due to the migration of neural crest tissue and proliferation of melanocytes during embryogenesis.3 Intense sunlight exposure, particularly ultraviolet B radiation, is a significant risk factor for development of cutaneous melanoma. Rates of melanoma are increasing significantly worldwide which is concerning due to its association with high mortality rates.4 Melanoma has variable biologic behaviour and significant metastatic potential. Most frequently, metastatic melanoma is detected in regional lymph nodes, lungs, liver and brain.5 Less than 5% of metastatic melanomas involve the gastrointestinal tract and of these, the majority are found in the small intestine.6 Rarely, metastases are identified in the gallbladder as documented in a number of case reports over the last few decades (Table 1).

Whilst metastatic spread of melanoma to the gallbladder is extremely rare, it still accounts for approximately 50% of metastatic lesions in this organ.5 The most likely metastatic pathway of cutaneous malignant melanoma to the gallbladder is haematologic spread.3 Although involvement is typically associated with widespread metastatic disease there are cases where melanoma metastases are limited to the gallbladder. These metastases may be present concurrently with the primary diagnosis or be identified decades later as the first indication of recurrence.20 In this case report, gallbladder metastases were the first site of metastases identified in the patient four years after their original melanoma diagnosis. Across the available literature, the time between melanoma diagnosis and gallbladder metastases varied significantly from synchronous detection to 20 years later.12,16,17,21 The type of melanoma, Breslow thickness, Clark level and sentinel lymph node biopsy status also varied significantly across case reports.

The majority of metastatic melanoma to the gallbladder is asymptomatic and will be detected incidentally or on surveillance imaging in patients with a history of melanoma. In an autopsy series, occult gallbladder involvement was identified in 15% of patients with disseminated metastatic disease.30 Given the discrepancy between the rate of detection at autopsy and the paucity of published cases, metastases to the gallbladder are evidently often asymptomatic.28 In approximately half of the available case reports, gallbladder metastases were detected on routine imaging in patients with known metastatic melanoma. The remaining patients were diagnosed after presenting with symptoms of either right upper quadrant pain, acute cholecystitis or jaundice. Radiographic investigations are often effective at identifying gallbladder masses. In most patients presenting with symptoms, USS and computed tomography (CT) were used to identify gallbladder metastases pre-operatively. Using USS, melanoma metastases are often identified as polypoid masses in the gallbladder without acoustic shadowing and are lower density than gallstones.31 On CT, they often seen as intraluminal masses or thickening of the gallbladder wall.32 In some cases, including the patient in this report, metastatic melanoma of the gallbladder is only identified incidentally on the histopathology after the cholecystectomy.
Table 1: Summary of existing case reports, including two case series.

| Author         | Year | cases | Age (Years) | sex | Detection             | Time since melanoma dx (month) | Cholelithiasis      | Melanoma characteristics | Other metastases | Surgery                          | Alternative management | Other management | Death |
|----------------|------|-------|-------------|-----|-----------------------|-------------------------------|---------------------------|------------------------|-------------------|----------------------------------|----------------------|-----------------|-------|
| Hess, 2020     | 1    | 62 M  | 60          |     | Routine imaging       |                               |                           |                        |                   | Pulmonary cholecystectomy         | CTx, RTx             |                 | No    |
| Hall, 2018     | 1    | 84 M  | 24          |     | Perforated acute cholecystitis | NR                           |                           |                        |                   | Pulmonary, liver, abdominal       | Yes within months    |                 |       |
| Saraswat, 2018 | 1    | 1     | 81          | M   | Acute cholecystitis    | "Several years"               | Not reported             | Subtotal cholecystectomy | Involved          | Sarawat, 2018                      | 1                    | 81 M            |       |
| Patel, 2017    | 1    | 50 M  | 12          | IV  | Ulcerated nodular      | -ve                           | T4N0M0                    |                        |                   | Laparoscopic cholecystectomy + hepatic wedge resection | Nil                  |                 |       |
| Antonini, 2016 | 1    | 73 F  | 48          |     | Routine imaging        | Not reported                  | Bladder                   |                        |                   |                                 | Not described         |                 |       |
| Kahn, 2017     | 1    | 57 M  | 2.7         | IV  | Ulcerated              | -ve                           | Nil                       | Laparoscopic cholecystectomy |                   |                                 | No                  |                 |       |
| Giannini, 2016 | 2    | 50 M  | 108         | IV  | Ulcerated nodular      | -ve                           | Spleen, brain, pancreas   | Laparoscopic cholecystectomy | RTx, ImmunoTx | Alive                          |                     |                 |       |
| Onozawa, 2014  | 2    | 40 F  | 24          | III | Nodular                | -ve                           | Liver, lung, intestine, bone | Laparoscopic cholecystectomy | CTx              |                                 | Yes within months     |                 |       |
| Christou, 2014 | 1    | 58 M  | 36          | IV  | Ulcerated malignant    | -ve                           | T3N0M0                    |                        |                   | Open cholecystectomy, wide wedge resection and regional LNBs | Nil                  |                 | No    |
| Furumoto, 2013 | 1    | 1     | 18          |     | Routine imaging        | Not reported                  | Nil                       | Laparoscopic cholecystectomy + partial liver resection |                   |                                 | No                  |                 |       |

Continued.
| Author, Year | Cases | Age, Years | Sex | Detection | Cholelithiasis | Time since melanoma dx (month) | Melanoma characteristics | Other metastases | Location | Surgery | Alternative management | Death |
|-------------|-------|------------|-----|-----------|----------------|-------------------------------|--------------------------|-----------------------|----------|---------|-----------------------|-------|
| Matsubayashi, 2012 | 1 | 82 M | ERCP | Imaging, ERCP | At time of diagnosis | Not reported | IV | T3N1M1 | Lung, liver | CTx | No | Ren en Y hepaticojunostomy and liver wedge resection | NR |
| Martel, 2009 | 1 | 45 M | Acute cholecystitis | At time of diagnosis | Abdomen | Regressed melanocytic lesion | | | | | | |
| Vernadakis, 2009 | 1 | 58 M | Acute cholecystitis | NR | 12 | Back | 3.8 | III | Superficial spreading | Brain | Exploratory laparotomy + cholecystectomy | CTx + ImmunoTx | Yes: 5 months |
| Sampleski, 2008 | 2 | 52 M | Biliary colic | Yes | 102 | Back | 1.3 & 0.7 | | Widespread subcut and LN | | Laparoscopic cholecystectomy | CTx | No: 36 months |
| Marone, 2007 | 1 | 54 | Routine imaging | 8 | Trunk | 6.1 | IV | Ulcerated | Mesentry | Laparoscopic cholecystectomy | | |
| Takayama, 2007 | 1 | 36 | RUQ pain | NR | 17 | Back | Not reported | | Peritoneal | Extended cholecystectomy | | |
| Tuveri, 2007 | 1 | 37 F | RUQ pain, fever | No | 12 | Right leg | 0.82 | II | Superficial spreading | Nil | Laparoscopic cholecystectomy | Nil | No |
| Van Bokhoven, 2006 | 1 | 66 M | Jaundice | 60 | Back | 1.6 & 2.5 | Involved | Ampulla of vater | Palliative care | Palliative stent | | NR |
| Safioleas, 2006 | 1 | 38 F | RUQ pain | No | Unknown primary | | | Brain | Open cholecystectomy | Refused | Yes: 4 months |
| Gogas, 2003 | 1 | 30 F | Routine imaging | 21 | Right arm | 3 | IV | Nodular | Nil | Laparoscopic cholecystectomy | | |
| Guida, 2002 | 1 | 32 F | RUQ pain | NR | 36 | Right shoulder | 1.9 | IV | | Brain | Open cholecystectomy with locoregional lymphadenectomy | CTx + ImmunoTx | Yes: 4 months |
| Langley, 1997 | 1 | 40 F | Acute cholecystitis | NR | 22 | Back | 0.3 | II | Superficial spreading | Liver, CNS | Laparoscopic cholecystectomy | CTx + RTx | Yes: 3 years |
| Katz, 2007 | 13 | 28-66 | 7 presented with biliary colic or cholecystitis | 0 | 39 months (0-248 months) | | 5 with isolated GB, 8 disease multiple sites | | Laparoscopic cholecystectomy: 9 | | |
| Dong, 1998 | 19 | 15 M, 4 W | Pain (10), Routine imaging (2) | 4/15 | Mean: 1.7 | 3-4 | Superficial spread (10), Nodular (3) | | Lap chole (11), cholecystostomy (2) | CTx 6 | Deaths: 14, Alive: 4 |

*NR: Not reported, *Median, CTx: Chemotherapy, RTx: Radiotherapy, ImmunoTx: Immunotherapy
Compared to primary gallbladder cancer where cholelithiasis is common, it is scarcely associated with metastatic melanoma. Interestingly, the patient in this case report had evidence of cholelithiasis and acute cholecystitis. The subsequent detection of metastatic melanoma was incidental. Only one other individual case study reported the presence of cholelithiasis and an incidental finding of metastatic melanoma after a laparoscopic cholecystectomy. In all other case reports where patients presented with symptoms, patients had no reported concomitant cholelithiasis. In the two case series, Dong et al. found 26.7% (4/15) of patients and in Katz et al case series no patients (0/13) had cholelithiasis.

Management of metastatic melanoma requires a multidisciplinary approach and may include surgery, adjuvant chemotherapy, immunotherapy and radiation oncology. There were significant discrepancies in treatment regimens across case studies, which is likely a reflection of the lack of current guidelines for management of patients with metastatic melanoma of the gallbladder. The survival benefit of surgical excision in patients with isolated gallbladder metastases and more widespread melanoma is unknown. However, surgery is usually beneficial for treating associated symptoms such as abdominal pain and acute cholecystitis. In the current case, surgery was indicated for management of the patient’s symptoms and diagnosis of gallbladder metastases was made pre-operatively. Where diagnosis of gallbladder metastases was made post-operatively, some case reports opted for a laparotomy or open cholecystectomy with or without resection of surrounding tissues. There was no consistency across reports regarding the indication for a particular surgical approach. Across the available case studies, approximately half of the patients proceeded to have chemotherapy or immunotherapy post-operatively and this appeared independent of whether the patient had other metastases. Whilst there are promising benefits of chemoimmunotherapy treatments such as high-dose interleukin-2, BRAF inhibitors and MEK inhibitors, their potential benefits for patients with metastatic melanoma of the gallbladder are currently unknown.

**CONCLUSION**

We present the case of a patient with acute cholecystitis with an incidental finding of metastatic melanoma. Our case report highlights the need for clinical suspicion of gallbladder malignancy in symptomatic patients with a past medical history of cutaneous malignant melanoma. Despite being a rare site of melanoma spread, as they are often asymptomatic, gallbladder metastases may be more common than initially reported. There are currently no gold standards for management of patients with metastatic gallbladder but a multidisciplinary approach including surgical and medical oncology input is often indicated.

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