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Case Report

Cholecystectomy for Resistant Metastatic Malignant Melanoma of the Gallbladder: A Case Report

Maria Julia Corbetta Machado^{1*} and Costa Karihaloo^{1,2}

¹ John Hunter Hospital, New South Wales, Australia

² University of Newcastle, New South Wales, Australia

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ABSTRACT

Malignant melanoma is an unpredictable disease, known to metastasize early even in thin melanomas. Historically the presence of intraabdominal metastasis meant poor prognosis with a 5-year survival of less than 20%. That has significantly changed with effective systemic therapy (EST), with most recent studies reporting 5-year survival of up to 50%. Metastasectomy for resistant disease has been considered in Stage IV disease, however there is very little literature on the combination of EST and metastasectomy. This report describes a case of Stage IV malignant melanoma patient who developed resistant disease within her gallbladder fundic wall. She underwent open cholecystectomy, with complete metabolic response at 1-year follow up PET.

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Case Report

A 78-year-old patient with metastatic melanoma from an unknown primary was referred by her oncologist to a General Surgeon for assessment of rapidly growing FDG avid gallbladder lesion seen on PET scan. Initially diagnosed with brain metastasis following computed tomography, she presented with neurological symptoms of gait instability and incoordination as her first disease signs. A 19mm right pontine lesion was identified, and further staging imaging subsequently organized. The initial PET scan showed multiple bilateral lung nodules and extensive subcutaneous disease, which prompted the presumptive diagnosis of metastatic melanoma. An excisional biopsy of one of the anterior abdominal wall lesions was performed, confirming the diagnosis. Pathology report consisted of malignant melanoma with wild type BRAF mutation.

Oral systemic treatment (temozolomide) in association with 6 weeks of radiotherapy consisted of her initial treatment cycle, followed by long-term Keytruda®. She completed 5 cycles of immunotherapy, with minimal side effects. Repeat PET showed excellent treatment response after treatment round with significantly decreased uptake from all deposits. There was no intra-abdominal uptake seen then. After being on

Keytruda® for 1 year, however, a single glucose-avid gallbladder spot appeared on PET (Figure 1). The patient was asymptomatic, and an ultrasound (US) was organized for further assessment. The US showed a thin walled gallbladder, with 2 to 3 hypodense areas measuring from 13 to 28mm confined to it. She was reviewed the following month with repeat PET and US, both showing significant increase in uptake (from 9U to 11U) and a clearly defined 75mm gallbladder mass confined to its mucosa (Figure 2).

The mass appeared to arise from the posterior wall, with a vascularized pedicle suspicious for neoplasm. She was subsequently referred to a general surgeon for opinion and management. She continued to deny abdominal pain, biliary colic and weight loss, with a fairly benign physical examination. Even though she had a significant history of metastatic melanoma, primary gallbladder malignancy needed to be excluded therefore further liver imaging was requested. An MRI of the liver was organized, and it showed a multilobulated mass lesion, measuring 7.5×3cm, confined to the gallbladder (Figure 3). Her tumor markers were negative (CEA, CA 19-9 and AFP), as were her liver function tests.

*Correspondence to: Maria Julia Corbetta Machado, M.B.B.S., John Hunter Hospital, Lookout Road, New Lambton Heights, New South Wales 2305, Australia; Tel: +61405225211; E-mail: majucorbettam@gmail.com

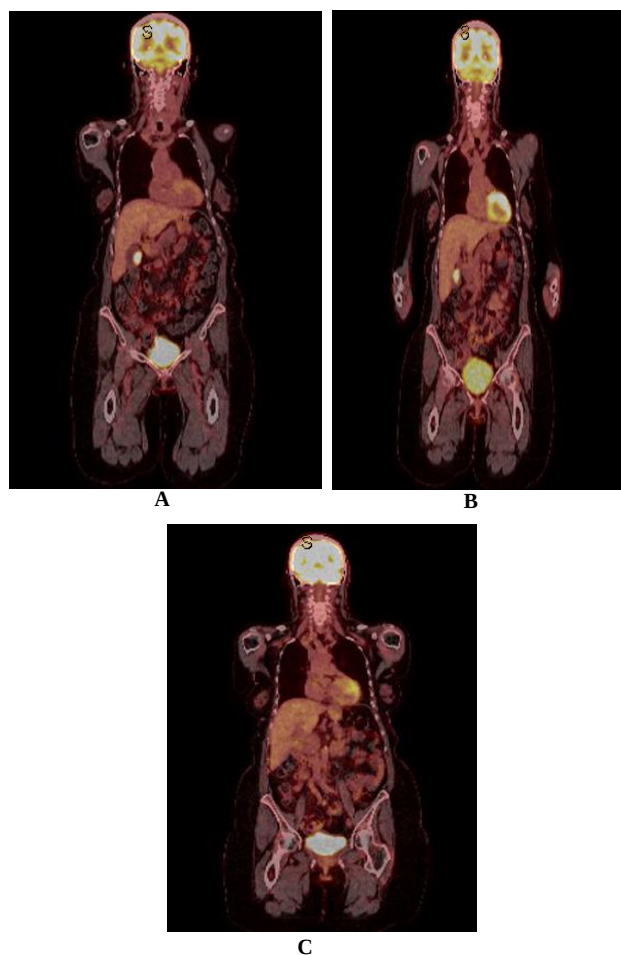


Figure 1: PET images **A)** Initial PET with diffuse gallbladder uptake **B)** Second PET with localized uptake to gallbladder **C)** Follow-up PET showing complete metabolic response at 1-year post cholecystectomy.



Figure 2: Biliary US.

Decision was made to undergo operative assessment with diagnostic laparoscopy followed by open cholecystectomy provided there was no gross intraperitoneal metastatic spread. Laparoscopy confirmed no macroscopic peritoneal disease, with a fairly normal looking gallbladder on inspection. An open cholecystectomy was done via right subcostal incision, macroscopic inspection of the specimen showed a 3cm black sessile mass protruding from the gallbladder fundus. The operation was uneventful, with the patient discharged from hospital day 3. The

pathology report confirmed ulcerated metastatic melanoma with a mitotic rate of 25, invading submucosa. Immunohistochemical staining was positive for BRAF and S100, negative for p16 (Figure 4). A 1-month postoperative follow up appointment was organized with a repeat PET that did not show further liver uptake. Immunotherapy was restarted then. The patient remains on immunotherapy, currently 13 months post cholecystectomy, with sustained complete metabolic response. Verbal consent to write this case report was obtained from patient by the authors.

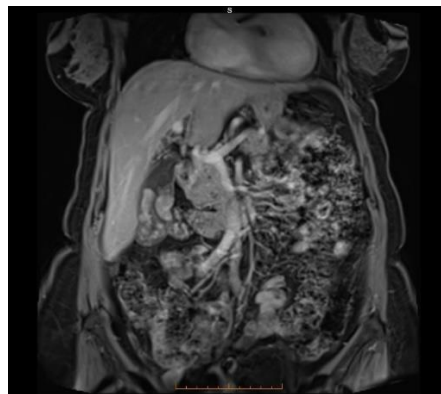


Figure 3: Liver MRI.

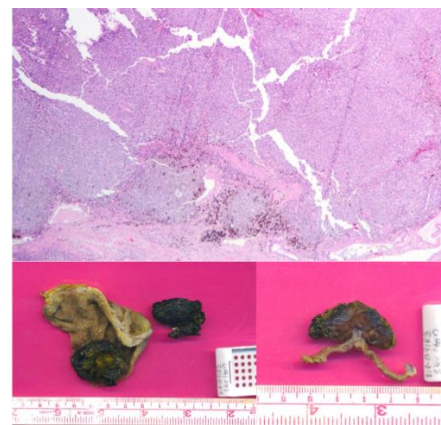


Figure 4: Histopathology report.

Literature Review

Melanoma is the third most commonly diagnosed cancer in the Australian population where approximately 4% of them present with Stage IV disease at time of diagnosis [1, 2]. This disease it is known to metastasize early, in even thin primary tumours. The most prevalent distant metastatic sites are brain and lung, followed by liver, bone and intestine [3]. Metastases are most commonly seen in the lung, whereas gastrointestinal metastasis only account for 2-4%. Even lower numbers are attributed to gallbladder deposits diagnosed in living patients [4-7]. Autopsy findings however have a significantly higher detection of gallbladder metastasis, with literature showing a range from 4 to 20% [6-8]. Virtually asymptomatic, the presence of gallbladder deposits is usually associated with widespread intra-abdominal disease, rarely presenting as an isolated tumour [4].

A case report published in 2009 however reported a patient who underwent open cholecystectomy for acute cholecystitis, where a clearly

melanocytic ulcerated mass was found. This patient had a background of previous melanoma resection from its back, and this incidental finding was attributed to the volatile nature of this disease. There is minimal to none evidence to why metastatic melanoma deposits of the gallbladder appear to be resistant to systemic treatment. In our case report, the patient interestingly presented with a new onset PET-avid lesion, resistant to immunotherapy. There is still limited literature about the role of metastasectomy in the current effective systemic therapy era, which is what makes this particular case report a valid start discussion point. Previous chemotherapy agents did not offer significant improvement in long-term survival, with median survival of 7-8 months reported in the literature [10]. Historically metastasectomy in selected patients offered the main survival benefit, being proven in several studies an increase in overall survival on those patients who underwent surgical resection regardless of palliative or curative intent [2, 10, 11].

Data published from MSLT-I reinforces the importance of surgical management on OS of stage IV melanoma patients, where patients who underwent surgical and systemic medical therapy had significantly higher 4-year survival (20.8%) compared to those who received systemic therapy alone (7%) [12]. However, only a small percentage of the patients on the MSLT-I study received the new effective systemic therapies – EST (i.e. targeted biological and immunomodulatory therapies). With the introduction of current EST stage IV melanoma patients' outcomes have improved significantly, with 5-year survival of 5 to 10% increasing to nearly 40% in recent years [2, 13, 14]. A recent paper published in 2017 analysed survival rates to patients who had EST alone versus those who had combination of EST and metastasectomy. Results showed a significant increase in 1 and 2-year survival rates with combination treatment [14].

Operative approach for metastatic gallbladder disease is still controversial, with some authors advocating for laparoscopic resection versus the traditional open [15, 16]. There is however little evidence comparing the 2 treatment options, with clear predilection for laparotomy found in older literature. With the progression of laparoscopic surgery, its role in this patient cohort is beginning to grow. The initial rationale for favouring laparotomy was for more accurate intra-peritoneal inspection when looking for concurrent melanoma deposits. A surgeon who is comfortable with its laparoscopic skills when performing a diagnostic laparoscopy nevertheless can easily achieve this. Laparoscopic resection has a well-established low complication rate and short recovery time, with some authors hypothesising that minimal surgical approach results in decreased tumour cell spread [16]. Laparoscopic surgery surely has its limitations, particularly with widespread omental caking and adhesions where the appropriate establishment of pneumoperitoneum might not be feasible. Other variable to be considered is the en-block resection of the gallbladder with its adjacent liver tissue. Usually only hepatobiliary surgeons will be comfortable in attempting such resection via this approach.

Conclusion

Malignant melanoma is an aggressive malignancy with early metastatic tendency with rare spread to gallbladder. Patients with resistant Stage IV disease involving gallbladder could benefit from metastasectomy

treatment. However, limited information about the best surgical approach in this patient cohort.

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