

CASE REPORT

Melanoma of the gallbladder: appropriate surgical management and review of the literature

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Key Clinical Message

Melanomas of the gallbladder (GB) are extremely rare with a very poor prognosis. They feature in the literature as a few case reports and the method of their management is not clear. We report a case of patient with metastatic cutaneous melanoma to the GB, and our treatment suggestion.

Keywords

Gallbladder, melanoma, metastasis, surgery.

Introduction

Melanomas of the gallbladder (GB) are extremely rare. They can be primary or secondary, both associated with very poor prognosis but cannot be differentiated histologically. Reports from autopsies show that the prevalence of secondary (metastatic) melanomas to the GB is between 15% and 20% [1, 2]. Nevertheless, from all the cancers metastasizing to the GB, melanomas appear to be the most frequent, accounting for about 50–67% [3, 4]. Primary melanomas of the GB feature in the literature as a few case reports and there is great controversy whether they are actual primaries or they are as yet undiscovered metastases [5]. Gastrointestinal metastases from melanoma primaries account for 2–4% of cases, with the most frequent sites being the small bowel (35–67%), large bowel (9–15%), and stomach (5–7%) [6]. We report a rare case of patient with cutaneous melanoma of the back, developing melanoma of the GB as the first site of

recurrence months after his primary, which was treated successfully with open cholecystectomy and wedge liver resection.

Method and Results

Written informed consent for publication of this case was obtained from the patient. A 58-year-old patient with Glucose-6-phosphate dehydrogenase (G6PD) deficiency and a history of primary melanoma of his back presented to our service. The patient was initially diagnosed with an ulcerated nodular malignant melanoma, Breslow thickness 2.20 mm invasive to Clark anatomic level IV. Following excision biopsy of the primary on 28 September 2010, he underwent wide local excision 2 days later. At the time of the wide local excision, a sentinel node biopsy was performed which was negative (final stage, pT3bN0MX). Following this, he underwent regular three monthly follow-up appointments with physical examination, chest

radiographs, and blood work including full blood count (FBC) urea and electrolytes and liver function tests.

In February 2011, the patient was admitted to the hospital with painful obstructive jaundice. An US of the abdomen showed dilatation of the common bile duct and a CT abdomen identified a “possible abnormality in the head of the pancreas”. An Endoscopic Retrograde Cholangiopancreatography (ERCP) was unsuccessful hence we performed a CT-guided FNA and core biopsy of the pancreatic abnormality. The ERCP was reattempted successfully with sphincterotomy, pancreatography, and biopsies taken from the ampulla of Vater. The pancreatography revealed a dilated pancreatic duct, normal biliary ducts, and a possible small pancreatic lesion close to the ampulla of Vater, which possibly caused the obstruction of the pancreatic duct. The histopathology results from the pancreatic FNA, pancreatic core biopsy, and the biopsy from the Vater were all negative for malignancy.

The patient’s pain and jaundice improved but the patient, against medical advice, decided to self-discharge before the results of the biopsies were back. He continued, however, the oncology follow-up.

By May 2011, he developed an enlarged left axillary lymph node and underwent axillary node dissection for stage III (N1b) disease. A bone scan performed at the time as part of his staging was unremarkable. Following surgery he received adjuvant postoperative radiotherapy, 50Gy in 20 fractions from July to August 2011. He then resumed three monthly follow-up visits.

In January 2012 his γ -GT was raised to 1.5X upper limit of normal. U/S of the liver showed no evidence of biliary obstruction or metastatic disease. As the γ -GT was persistently elevated (2 \times upper limit of normal) a brain, chest, abdomen, and pelvis CT was performed early in 2013. This showed a lesion in the GB with accompanying lymphadenopathy of the celiac axis and liver hilum.

This was confirmed with an US of the abdomen. Neither examination showed hepatic metastases (Fig. 1).

An abdomen Magnetic Resonance Imaging/Magnetic Resonance Pancreatography (MRI/MRCP) verified an intraluminal ill-defined lesion of the corpus of the GB compatible with a tumorous opacification associated with regional lymphadenopathy of the liver hilum and no evidence of liver metastases (Fig. 2).

In view of the above, the patient was admitted for a planned open cholecystectomy and wide wedge resection of the liver and regional lymph node dissection as a combined procedure in March 2013. Intra-operatively great



Figure 1. CT abdomen showing the suspicious lesion in the gallbladder.

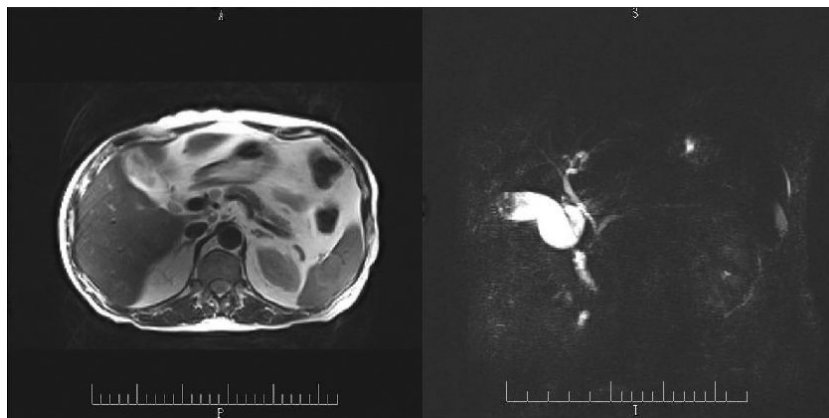


Figure 2. MRI/MRCP confirming the suspicious intraluminal lesion.

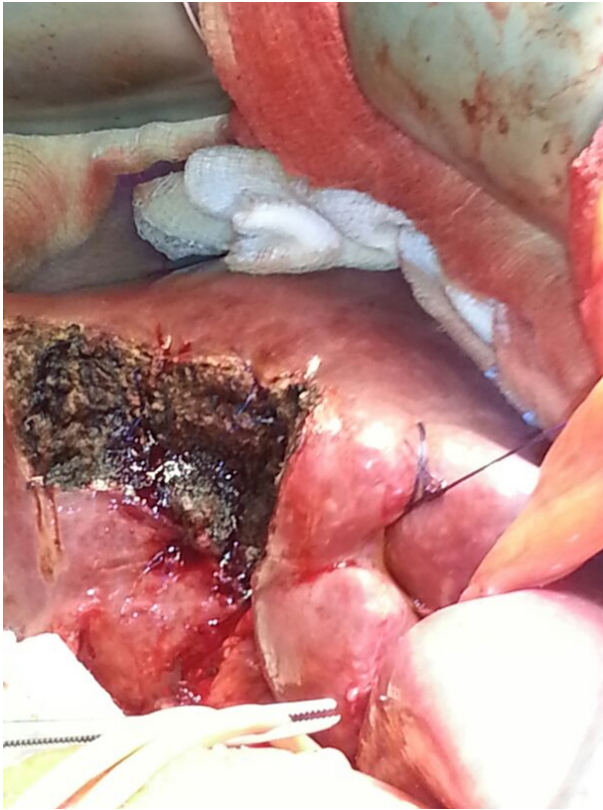


Figure 3. Open cholecystectomy and wedge liver resection.

care was taken to minimise manipulation of the tissues in order to avoid any contamination of the abdominal cavity. A manual exploration of the bowel tract to detect any intraluminal or serosal implants was performed to complete the operation. He had an uneventful recovery from the operation and was discharged home (Fig. 3).

Macroscopic evaluation of the GB showed a vegetative fragile soft lesion adherent to the mucosa projecting into the lumen measuring $3.5 \times 2 \times 2$ cm. Microscopy revealed a malignant tumor necrotic in some areas. The malignant cells were medium-sized amorphous atypical cells with large eosinophilic cytoplasm, vesicular nucleus

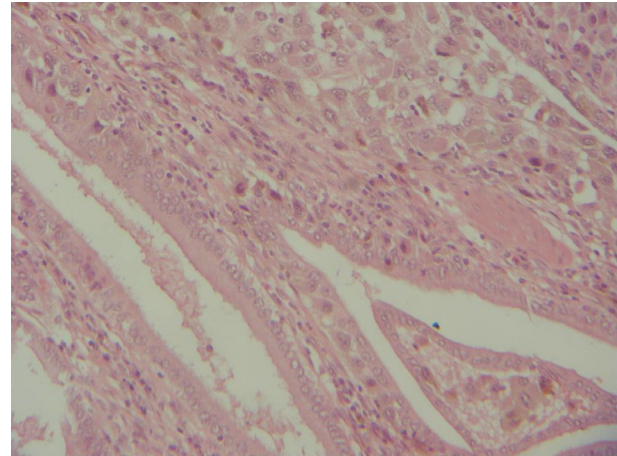


Figure 4. H&E of the specimen.

and prominent nucleolus, and infiltrated the muscularis externa of the GB. There was also perineural invasion. Immunohistochemistry showed positivity for HMB45 and MelanA confirming the diagnosis of metastatic malignant melanoma with high cellular polymorphism. The corresponding hepatic specimen was free of metastasis. There were also no metastases to the hepatoduodenal regional lymph node (Fig. 4 and 5).

No other adjuvant therapy – for example, with high-dose interferon– was deemed appropriate in accordance with the most recent guidelines for malignant melanoma. [7] A new baseline follow-up CT of brain, chest, abdomen, and pelvis and a bone scan 2 months postoperatively showed no evidence of disease recurrence. At the most recent follow-up, clinic evaluation 6 months after surgery the patient was well without evidence of recurrence.

Discussion

Melanomas of the GB are extremely rare. Whether primary or secondary, histopathologists have great difficulty distinguishing between the two. The first case of primary

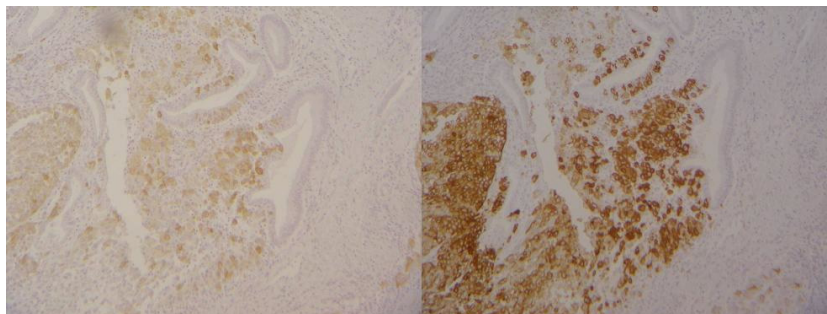


Figure 5. Positivity for HMB45 and MelanA confirming gallbladder melanoma.

melanoma of the GB mucosa was described by Wieting and Hambi [8]. Since then, only a few sporadic cases of primary melanomas of the GB have been described in the literature. The potential of melanoma to develop from the visceral mucosa is suggested by many authors who indicate that migration of melanocytes from the neural crest to the endoderm during the embryonic growth is possible.

Hematologic spread is the likely metastatic pathway for melanomas of the GB. The presence of a past history of cutaneous malignant melanoma suggests the diagnosis of a metastatic lesion. Although rare in its entity, metastatic melanoma to the GB appears to be the most frequent in this organ, accounting for the majority of all the reported cases. Most authors believe that melanoma in the biliary tract is almost always a metastasis, with potential primary sites being skin, oral cavity, anorectal region, uveal tract, and meninges [9]. This is reinforced by the fact that 15–20% of patients that die from disseminated melanoma have metastasis to the GB [9].

The distinction between primary GB melanoma and a solitary metastasis to the GB from a malignant melanoma that arose elsewhere (e.g., skin, other mucosal site) is likely to be only of academic importance. In the absence of other metastatic disease, the mainstay of treatment is surgical resection. The main surgical issue is when and how best to remove the lesion. Another issue is the extent of surgical resection that ought to be undertaken. When melanoma of the GB is identified incidentally after cholecystectomy, this should prompt towards the search of a primary site in the skin or other mucosal surfaces. The absence of a clear primary site should then direct the clinician toward the diagnosis of primary GB melanoma.

Both primary GB melanoma and metastatic melanomas to the GB have similar presentations. Most patients are asymptomatic and lesions are identified incidentally. Other presentations are those which, mimic acute cholecystitis such as right upper quadrant or epigastric pain and nausea or vomiting. Obstruction of the cystic duct by the tumor in the absence of cholelithiasis can lead to obstructive jaundice, just like in our patient. This presentation usually points toward the provisional diagnosis of choledocholithiasis and delays the diagnosis of GB lesion with unnecessary investigations like ERCP, if primary imaging investigations fail to suggest intracholecystic lesions.

The initial investigation of choice is an US scan of the abdomen. The scan can reveal GB wall thickening, an intramural mass if greater than 1 cm without acoustic shadow and distinguish between stones and probable benign small polyps [10–12]. The only drawback to this investigation is that it is user dependent and small lesions that may grow rapidly in only a few months will be missed initially. This probably happened with our patient

who presented initially with obstructive jaundice and the US was reported “unremarkable”. Another possible reason for the initial jaundice in our patient that improved spontaneously may be tumor necrosis which leads to its sloughing thus causing intermittent blockage of the common bile duct. Another theory that is suggested in the literature is that malignant melanoma can spontaneously regress hence early diagnosis is missed [13 14].

CT, MRI and Positron Emission Tomography (PET) scans show similar findings with the US scan with the difference that the results can be more reliable since the images are not user dependent and can reveal distant unexpected metastases [15]. Oral or intravenous cholecystography, and ERCP give images that can predict GB filling defects, however they can easily miss subtle defects. Generalizing, radiologic findings of malignant GB tumors are varied and a strong suspicion is required to avoid missing an important diagnosis.

The differential diagnosis of intraluminal GB lesions includes primarily adenocarcinoma of the GB which is much more common than GB melanoma [16]. GB adenocarcinoma is commoner in older women unlike GB melanoma, which is more common in middle-aged men. Also adenocarcinoma is associated with cholelithiasis unlike melanoma. Other much less common diagnoses can be small cell carcinoma, squamous cell carcinoma, carcinosarcoma, and lymphoma [16]. Renal cell carcinoma can also hematogenously metastasise to the while hepatocellular carcinoma can be locally invasive. Benign lesions such as cholesterol polyps, inflammatory polyps, adenomyomatosis, and adenomatous polyps are also included in the differential diagnosis list.

Because of its rarity, melanoma of the GB should always be suspected in a patient with a past history of cutaneous malignant melanoma who presents with hepatobiliary symptoms. The prognosis of both primary and metastatic disease is very poor. The mean survival rate for patients with primary lesions documented is 20.1 months and for those with metastatic lesions 8.4 months [17]. Anecdotal reports in the literature of completely resected metastatic melanomas of the GB as the first site of recurrence, document prolonged survival of up to 100 months [18].

From 1996 to 2006, the National Cancer Institute of Naples recorded 1684 patients with the diagnosis of cutaneous melanoma, which was surgically treated [19]. Of these, 30 (1.7%) developed metastatic lesions to the GI tract requiring surgical exploration but only one patient developed a GB metastasis as the first site of recurrence. In view of the rarity of the disease and the lack of adequate evidence, the treatment options are unclear. Generally, it is accepted that primary or isolated metastatic melanomas of the GB should be aggressively treated with

surgery that will generally prolong survival and improve the prognosis. Dong *et al.* reported a 100% survival at 1 year in patients who had surgery for isolated GB metastases compared with 0% for those with unresectable tumors with multiple metastases [18]. Nevertheless, even if there is disseminated metastatic disease, surgical removal of the GB seems to be a worthwhile palliative procedure as concluded by Katz *et al.* [20]. The question that follows is whether conventional or laparoscopic cholecystectomy should be performed. Seelig *et al.* and Taveri *et al.* both treated one patient each with isolated metastatic melanoma of the GB using laparoscopic cholecystectomy with excellent results and survivals reaching 20 months and 60 months, respectively, concluding that laparoscopic cholecystectomy is sufficient [21, 22]. Kohler *et al.* concluded that since all melanomas of the GB seem to be confined intraluminally, the operation should be carried laparoscopically and lymphadenectomy in the region of the hepatoduodenal ligament does not appear to be appropriate [23]. Katz *et al.* reported a series of 13 patients with the diagnosis of melanoma metastatic to the GB [20]. Of those, 3 had laparoscopic cholecystectomy 2 of which later developed port site recurrence even if great care was taken to avoid dissemination of cancerous cells during retrieval of the GB. Jean Pierre *et al.* reported a patient who underwent radical open cholecystectomy with survival reported being 18 months at the date of the publication [24]. We suggest open cholecystectomy rather than laparoscopic in order to firstly avoid trocar recurrence and also to maximise the detection of liver or bowel secondaries unidentified by conventional imaging techniques.

The other issue is the extent of surgical dissection. We performed wedge liver resection and avoided extensive regional lymph node dissection despite the preoperative imaging results that suggested lymphadenopathy in the celiac axis, hepatoduodenal ligament, and liver hilum. Local invasion of the GB wall toward the liver is sometimes seen and this is our justification for wedge liver resection. We avoided extensive regional lymph node clearance and only removed suspected lymph nodes in the area because there was no clear palpable evidence of lymph node infiltration intraoperatively.

The last issue that is not clear for malignant melanoma of the GB is the role of systemic therapy. Before 2011, no systemic treatment for stage III or stage IV melanoma had been consistently proved to increase median survival, which remained in the range of 8–11 months. High-dose Interleukin-2 has shown tumor remission in approximately 15% of patients but it can only be used in a very few selected patients because of toxicity and difficulties with its administration [25]. Recently the advent of the immunotherapy drug ipilimumab (Yervoy) and the *b-raf*

inhibitor vemurafenib (Zelboraf) have shown to be more effective and improved survival in phase III trials [26–28]. There is, however, need for further studies.

Conclusion

Melanoma has the ability to metastasize extensively, with aggressive course and poor prognosis. Gallbladder metastasis of melanoma is considered a rare event, especially as an isolated lesion and the first site of recurrence. Biliary symptoms in a patient with prior history of malignant melanoma should alarm bells for a possible metastasis and prompt investigations should be carried out. Primary melanoma of the GB, even though again very rare, is also a possibility and should be born in mind in intracholecystic lesions of greater than 1 cm. Open cholecystectomy and wide wedge liver resection seems to give a combined therapeutic and diagnostic approach, allowing the removal of the tumor and also the manual exploration of the rest of the abdominal viscera for undiscovered metastatic lesions.

Conflict of Interest

None declared.

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