ABSTRACT Malignant melanoma of gallbladder is a rare entity; mostly, it is metastatic in nature. Primary malignant melanoma is extremely rare. In this article, we have presented a case of primary malignant melanoma of gallbladder that was treated successfully by surgery. Presentation of primary gallbladder melanoma is no different from other gallbladder malignancies; diagnosis is purely based on histology or cytology. Surgery is the mainstay of treatment, though multiple systemic therapies are under trial. Overall prognosis is poor with some exceptions.

KEYWORDS Malignant melanoma, Gallbladder, Mucosal melanoma

Introduction

Melanoma, as the name suggests, is a tumor arising from the malignant transformation of the melanocyte. Melanocyte precursors arise from the neural crest and as the fetus develops, migrate to multiple areas in the body[1]. Melanoma can arise from any of these locations through the malignant transformation of the resident melanocytes. By far the most common location is the hair-follicle bearing skin and dermo-epidermal junction[2] followed by ocular and metastatic melanomas. Malignant melanoma is 5th most common United States cancer diagnosis[2]. In India, the incidence of melanoma is comparatively low due to dark skin complexion.

Melanoma of gallbladder is a rare entity; mostly, it is secondary. Malignant melanoma rarely metastasizes to gallbladder but, among metastatic tumors of the gallbladder, melanoma is most common. Gallbladder metastasis is seen in 15-20% autopsies of patients with malignant melanoma[3]. Hematological spread is the likely metastatic pathway[4]. Primary malignant melanoma of gallbladder is very rare.

Gallbladder melanoma was first described in 1907 [5] based on autopsy findings of a 40 years old female. Later on, Metastatic and primary gallbladder melanoma have been reported sporadically several times in the past [1,3-8]. One of largest case series of melanoma of gallbladder was published in 2000 by Dong XD et al. comprising of 19 cases out of which one was primary and remaining cases were metastatic in nature.[5]

Case report

An 80 years old female patient presented with complaints of dull aching right hypochondriac pain associated with occasional bilious vomiting for a period of 15 days, apart from this patient had no other complaints. There was no other significant past, family or personal history. Mild tenderness was present in the right hypochondrium.

Ultrasound abdomen showed two polypoidal mass lesions in the gall bladder, one in the fundus measuring approximately 44mm×30mm in size(Fig. 1A) and other near the neck measuring 31mm×24mm in size(Fig. 1B). Liver function tests of the patient were within normal limits.

Further, contrast CT abdomen and pelvis(Fig. 2A & 2B) showed a soft tissue density mass measuring 2.8cm×2.7cm×3.2cm in gall bladder lumen on the peritoneal side not extending beyond the gallbladder suggestive of gall bladder malignancy with cholelithiasis. The liver was normal without any liver abnormality. No clinical data suggesting liver metastasis was obtained.

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X-ray was clear without any signs of metastasis. CA19.9 was 129.19U/ml.

A diagnosis of the carcinoma gall bladder was made, and the patient was subjected to open radical cholecystectomy. Intra-operatively there was a polypoidal lesion in the lumen measuring 4cm×3cm×3cm on the peritoneal side, and the lesion was not extending beyond gallbladder, cystic duct and common bile ducts were grossly normal. Liver, other abdominal viscera and pelvis were normal. On pathological study there was a polypoidal lesion in the lumen measuring 4cm×3cm×2.5cm on peritoneal side of the gallbladder, cut surface of the polyp was greyish brown and friable.

Microscopic sections revealed a malignant neoplasm composed of large polygonal and spindle cells arranged in a dissociated manner with prominent nucleoli. A large amount of melanin pigment was seen both intra and extracellular(Fig. 3). Tumor infiltrated the wall of the gallbladder and invaded perimuscular connective tissue, but no extension beyond the serosa was seen. No lymphovascular emboli or perineural invasion was seen. Gall bladder neck resection margin and the underlying liver bed were free of tumor. All lymph nodes (13 lymph nodes were resected) were negative for metastasis. Tumor cells were positive for HMB-45 on immunohistochemistry, confirming the diagnosis of melanoma(Fig. 4).

TNM class pT2b, pN0, cM0. Stage I.ib.

After diagnosing malignant melanoma of gallbladder search for another site, melanoma was done. On physical and ophthalmic examination, there was no evidence of cutaneous or uveal melanoma. Due to non-availability of PET scan, CT thorax and MRI brain were done, which showed no metastatic lesions. Considering the age of the patient and R0 resection with good tumor-free margins and no lymph node involvement patient was not subjected to adjuvant therapy and was kept on regular follow up with physical and ophthalmic examination, ultrasound whole abdomen and serum S100 levels every two months. By the end of one year patient is asymptomatic without any recurrence.

Discussion & literature review

Melanoma of gallbladder is a rare entity; most of the cases are metastatic and primary are extremely rare. There is no estab-
published literature on incidence, diagnosis, management and the staging of melanoma of gall bladder. As many as 50% of gall bladder malignancies are detected after simple cholecystectomy[9]. Since malignant melanoma of gall bladder is a rare entity, its diagnosis preoperatively is very unlikely, and it is almost always diagnosed after FNAC or biopsy or after examination of the surgical specimen. Clinically it is indistinguishable from other gallbladder cancers. In general, mucosal melanomas are associated with a higher risk of local recurrence, regional nodal metastasis, distant metastasis and death[2].

Ultrasound is the most frequently used initial diagnostic modality. Daunt, and King had first described the Ultrasound appearance of metastatic melanoma in the biliary tree as an atypical polyloid lesion without acoustic shadow. Later, the importance of color Doppler was emphasized by Avila et al., who noted an intravesicular mass with the documented vascular(HMB-45, S-100, tyrosine, Malt1/MelanA). Immunohistochemistry and lymph node metastasis that are borderline in size[10], the tumor for resectability, detection of small bowel metastasis or metastatic). A PET-CT scan is also helpful in assessing lesions of more than 5mm; Exception is uveal melanoma (primary or metastatic) may be indicated to evaluate known areas of metastasis or to evaluate symptoms. PET scan is sensitive to detect metastatic disease, and differentiating tumor and previous surgical scar[2]. Diagnostic laparoscopy is recommended to identify radiologically occult metastasis, particularly peritoneal implants[11].

Staging of mucosal melanoma of gastrointestinal tract and female genital tract are not included in the AJCC staging system of malignant melanoma.[12] Thus, the staging system recommended by AJCC for adenocarcinoma of the gallbladder can be used for staging of melanoma gallbladder.

Surgical resection is the primary modality of the treatment for cutaneous as well as primary mucosal melanomas[2], and this general rule can be applied to melanomas in the gallbladder as well.

If the malignancy is diagnosed pre-operatively, the surgical clearance must be attempted with wide margins. But as many as 50% cases of gallbladder malignancies (which include melanoma) are diagnosed after the gallbladder is removed for benign causes. Since the serosal surface of the gallbladder on the side attached to the liver is absent thus simple cholecystectomy may not remove T2 tumor completely even though such tumors are considered to be confined to gallbladder[12]. Therefore, such cases require revision surgery to achieve R0 resection, as data suggests that surgical clearance improves survival.

In the case of metastatic melanoma of gallbladder, selected cases may benefit from surgery. For some, it is palliative and may be curative in rare cases. Berger AC et al. suggested that for metastatic gastrointestinal melanomas (mostly referring to intestinal metastasis) if the patient can be rendered surgically free of disease, then there may be long term survival of more than five years in as many as 25% of patients and mean survival is more than two years[13]. Considering these findings, it may be advisable for patients with metastatic melanoma gallbladder to subject for surgery if the patient can be rendered disease-free with acceptable morbidity.

In case of an advanced metastatic/ primary melanoma of gallbladder, the likely complication would be obstructive jaundice. In such cases ERCP guided stenting, and percutaneous trans-hepatic biliary drainage are generally primary resorts to relieve obstructive jaundice. Haemorrhage from metastatic lesions

Figure 2 B: Contrast CT abdomen, transverse section: shows Soft tissue mass in gallbladder lumen on peritoneal side, lesion limited to gallbladder.

Figure 3: Histopathology of gallbladder: Note the prominent nucleoli and presence of both intracellular and extracellular melanin deposition.
somatic BRAF mutation in management is the determination of BRAF mutational status. BRAF and MEK inhibitors are approved for the treatment of only patients expressing mutant BRAF at position V600. This is because preclinical studies have shown that BRAF inhibitors are not only ineffective in patients not showing BRAF V600 mutation but also detrimental to the patients by activating the MAPK pathway and increase cancer progression[15-18].

In cases where systemic therapy induces a partial response, surgical resection of the residual disease may be feasible to render the patient clinically free of disease.

Patients with multiple asymptomatic visceral metastases are the candidates for systemic therapies rarely surgery may be attempted in cases with prior failure of systemic therapy, young patients for whom peri-operative morbidity is not primary concern and disease that is particularly amenable through limited surgery[2].

Laparoscopic approaches have been attempted, and few reports have shown equivalent results in comparison to open surgery. However, open surgery is preferred as it gives the added advantage of manual exploration of the gut to reveal metastatic bowel lesions which are not identifiable in preoperative imaging.[1]

Adjuvant therapy is controversial. In general, for other primary mucosal melanomas, adjuvant local post-operative radiation therapy with approximately 60, 66 and 70 Gy conventionally fractioned for R0, R1 and R2 resection. Its role in the gallbladder is unknown. This may improve local control when widely clear margins are not feasible[14].

Selected Patients of mucosal melanomas (cases with thick mucosal lesions with or without lymph nodes involved) can be subjected to postoperative interferon therapy trials, but the response is not proven. These patients may also be eligible for a clinical trial in the adjuvant settings[2].

In the case of advanced melanomas, the primary decision point in management is the determination of BRAF mutational status. BRAF and MEK inhibitors are approved for the treatment of only patients expressing mutant BRAF at position V600. This is because preclinical studies have shown that BRAF inhibitors are not only ineffective in patients not showing BRAF V600 mutation but also detrimental to the patients by activating the MAPK pathway and increase cancer progression[15-18].

New effective systemic therapies[19] including CTLA-4 blockers, BRAF/MEK inhibitors may be the alternatives for management of patients with tumors that are too extensive to resect. However, a multidisciplinary team assessment is advised to weigh the short term risk of delaying surgery against the possibility of significant systemic tumor regression with these therapies. Detailed insight into various systemic therapies under trials is beyond the scope of this article.

Adaptive cell therapy is gaining importance in recent times. It is a kind of immunotherapy in which antitumor activity is infused into tumour-bearing cells, and consequently, tumor antigens are detected, and cancer cells are destroyed. 50-70% of patients with metastatic melanoma experience objective cancer regression by Response Evaluation Criteria in Solid tumors when treated with Adaptive cell therapy [20, 21].

German S3 guidelines[22] or National Comprehensive Cancer Network(NCCN) V3.2020 guidelines can be used for follow up of melanoma[23]. The clinician may choose guidelines for stage IV disease for primary melanoma of gall bladder as it is more aggressive than metastatic melanoma of gallbladder.

Prognosis of both primary melanomas of the gallbladder and metastatic melanoma of gallbladder is very poor. Christou D. et al. showed a mean survival of 20 months in primary cases and 8.4 months in metastatic cases[5]. Dong, X.D. et al. said in their report that the only primary case among the 19 reported cases survived for 13.5 months and cases with widespread metastasis had 0% survival at the end of 1 year. Isolated resectable metastatic cases had 100% survival after one year. Only one survived for 13.8 years which is probably one of the longest survival of melanoma of gallbladder patient.[5]

**Conclusion**

Melanoma of gallbladder is a rare tumor. Suspicion should be made in patients with cutaneous or mucosal melanomas with biliary symptoms. Diagnosis is always based on histology or cytology. Thorough workup should be done to locate undetected cutaneous, ophthalmic, mucosal or visceral melanomas. Surgery is the mainstay of treatment in either primary or metastatic cases, and systemic therapies can be tried in unresectable cases in consultation with a multidisciplinary team. The overall prognosis of malignant melanoma of Gallbladder remains poor and is worst with widespread metastasis.

**Abbreviations**

- CT- Computed Tomography
- PET- Positron Emission Tomography
- MRI- Magnetic Resonance Imaging
- FNAC- Fine Needle Aspiration Cytology
- AJCC- American Joint Committee on Cancer
- ERCP- Endoscopic Retrograde Cholangiopancreatography

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