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Primary gallbladder melanoma: A systematic review of literature

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ABSTRACT

Primary gallbladder melanoma (PGM) is a rare malignancy with only sporadic cases reported in the English literature. We performed a systematic review of the cases published in the PubMed, Science Direct and Google Scholar databases with the aim of describing the reported clinicopathologic features of PGM. Thirty-six articles reporting on 39 patients were reviewed. There was a male predominance, with 23 (64 %) of 36 patients being males. The mean age at presentation was 55 ±16 years. Pain in the right upper quadrant was reported in 20/27 (74 %). The average size of the tumor was 3.5 × 1.9 × 1.4 cm. Gallbladder calculi were reported in 7/27 (26 %). A cholecystectomy was performed in 34/38 (89.5 %). Grossly, the tumor mostly (96.5 %) had polypoid appearances and on microscopic examination, the tumor were predominantly comprised of epithelioid cells 12/17 (70.6 %). Mitotic figures and prominent nucleoli were reportedly found in 8/8 (100 %) and 3/3 (100 %) respectively. Junctional melanocytic components were present in 13/21 (61.9 %). Tumor cells were reportedly immunoreactive for S-100 and HMB-45 in all tested cases. Metastasis were reported in 25/36 (69.4 %), with lymph nodes being the most common site ($n = 8$), followed by brain ($n = 6$) and liver ($n = 4$) for metastasis. At a mean follow-up period of 19 +/− 3 months, 16 (48.5 %) of the 33 patients with available survival data were alive and 17/33 (51.5 %) were dead of disease. There is a lack of unified criteria for the diagnosis of PGM, and future studies should aim to resolve this.

1. Introduction

Primary gallbladder melanomas are extremely uncommon. In published reports of such occurrences, there is debate concerning the existence of this basic entity [1,2]. Wieting and Handi [3] recorded the first primary gallbladder melanoma in 1907, and Walsh [4] reported the first histologically verified case of primary gallbladder melanoma fifty years later. Since then, there have been further cases reported of primary melanoma of the gallbladder [1,4-38]. Metastatic malignant melanomas are much more common. Following the initial belief that these metastases are uncommon in the gastrointestinal tract (GIT), accumulating evidence suggests that they account for 15 % of gallbladder metastases [39]. Although gallbladder metastases are uncommon, malignant melanoma accounts for 50–60 % of them [6,28]. The most contentious issue is histogenesis, or the possibility of this basic entity. Ricci et al. [28] discovered melanocytes, both normal and malignant, in malignant gallbladder melanoma. In the scientific literature, only occasional cases of primary pulmonary gallbladder melanoma (PGM) have been reported, primarily as single case reports.

Melanoblasts are yet to be established in organs of endodermal origin [10], and because the gallbladder is an endodermal offshoot, melanoma is unlikely to emerge from this organ or other visceral structures. On the other hand, non-neoplastic melanoblasts are the result of melanin-producing cells migrating from the neural crest to endodermal derivatives during embryologic development, which explains the presence of melanocytes within their mucosa [1] and supports the possibility of

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developing primary melanomas at these sites [39]. Therefore, primary gallbladder melanoma is theoretically plausible [2,22]. Although primary melanoma of the gallbladder is still a controversial clinical entity, studies on this subject continue to accumulate [1,4-38]. As a result, there is currently little data on the clinical, pathological, and molecular characteristics of these tumors. We conducted a thorough assessment of recent literature with the goal of describing the clinical manifestations, pathological and diagnostic aspects, therapeutic options, and prognostic results observed in PGM patients.

2. Materials and methods

A study of the published literature on primary gallbladder melanoma cases was conducted. As this study met the standards for non-human subject research, no board permission was required.

2.1. Search strategy

A systematic review was conducted in accordance with the guidelines on the preferred reporting items for systematic reviews and meta-analyses. The authors conducted a search of PubMed, Science Direct, and Google Scholar using the search term "Primary Gallbladder Melanoma," with no time limit included, where a consensus about the diagnosis of primary gallbladder melanoma was achieved with histopathology, comprehensive physical examination, and clinical acumen. "(Primary) OR (primary)" AND "(Gallbladder Melanoma) OR (Gallbladder Melanomas)" were the MeSH words. The investigation was completed on November 23, 2023. Human subject and English language articles were included in the study. When the inclusion criteria were met, all abstracts were evaluated and full-text publications were obtained. Studies and publications with insufficient or partial data are barred.

2.1.1. Selection criteria

We initially planned for larger studies; however, because our initial search yielded only case reports and case series on primary gallbladder melanoma, our updated inclusion criteria were observational studies (case series and case reports). Primary gallbladder melanoma studies with data on the diagnosis, evolution, treatment, and follow-up were included. Non-English language and animal studies were also excluded. Non-availability of full-text research and studies with insufficient data were also omitted. The search review and analyses were performed independently by two researchers. Any differences were determined through discussions with all the authors. The list-wise elimination procedure was employed if any of the variables evaluated had missing data. (In cases where some variables had missing values, only cases with all or almost all variables in the analyses were used). Quantitative analysis was performed by merging the data in each metric's original metric.

2.1.2. Data extraction

The variables included author, year of publication, study type, patient demographics, pigment lesions, diagnosis, and follow-up. Data analysis was performed using Microsoft Excel 2018 (Microsoft Corp., Redmond, WA, USA).

2.1.3. Data analysis

Statistical Package for the Social Sciences (SPSS) software (version 20.0; IBM (SPSS Inc., Armonk, NY, USA) was used for the analysis. The statistical analysis included 33 cases of primary gallbladder melanoma with survival data. Survival was defined as months from diagnosis to death or last follow-up. Patients who were still alive at the time of the last follow-up were considered censored. The total distribution was estimated using the Kaplan-Meier method, as shown in Fig. 2. Microsoft Excel 2018 (Microsoft Corp., Redmond, WA, USA) was used for analysis.

3. Results

PubMed, Science Direct, and Google Scholar searches were performed with 305 articles (Fig. 1). A total of 36 case reports/case series with a sample size ($n = 39$) were included. Table 1 shows the main clinical, pathological, and prognostic data reported in the reviewed articles.

3.1. Gender

Data was available for 36 patients, of whom 13/36 (36 %) were females and 23/36 (64 %) were males. Data was not available in 3 cases.

3.2. Age

The average was 55 +/− 16 years, with a range from 29 to 80 years. The mean age for females was 56.5 years and for males 54.5 years.

3.3. Ethnicity

Data were available for 7 patients, with Caucasians patients being the most common with 6/7 (85.7 %), followed by 1/7 (14.3 %) patient from Japan however 32/39 (82 %) of the cases, did not report the race.

3.4. Pigmented lesions on skin

Pigmented lesion on the skin were present in 6/30 (20 %) cases. In 24/30 (80 %) cases it was absent and 9/39 (23 %) cases it was not reported. Pigmented Lesions were found on the skin of right upper arm ($n = 1$), shoulder ($n = 2$), back (n = 1), chest (n = 1) and forehead (n = 1).

3.5. Symptoms at presentation

Pain in right upper quadrant was reported in 20/27 (74 %) cases. It was absent in 7/27 (26 %) cases. Nausea and Vomiting was reported in 12/25 (48 %) cases. It was absent in 13/25 (52 %) cases.

3.6. Size of tumor

Size of the tumor was reported in 24/39 (61.5 %) cases. The size of tumor was not mentioned in 15/39 (38.46 %) cases. Size of tumor in three dimensions was reported in 13/24 (54.2 %) cases and in one dimension in 11/24 (45.8 %) cases. The average three dimensional size of tumor was reported 3.5 × 1.9 × 1.4 cm and the average size of tumor reported in one dimension was 2.84 cm.

3.7. Follow-up

The mean follow-up for patients was a total of 19 months, for females at 11.7 months, and for males at 24.6 months.

3.8. Gallbladder calculi

Gallbladder calculi were reported in 7/27 (26 %) cases. In 20/27 (74 %) cases they were absent. They were not reported in 12/39 (30.7 %) cases.

3.9. Cholecystectomy

Cholecystectomy was performed in 34/38 (89.5 %) cases. It was not performed in 4/38 (10.5 %) cases.

3.10. Gross findings

Grossly, the tumor had polypoid shape in 28/29 (96.5 %) and papillary shape in 3/23 (13 %) cases.

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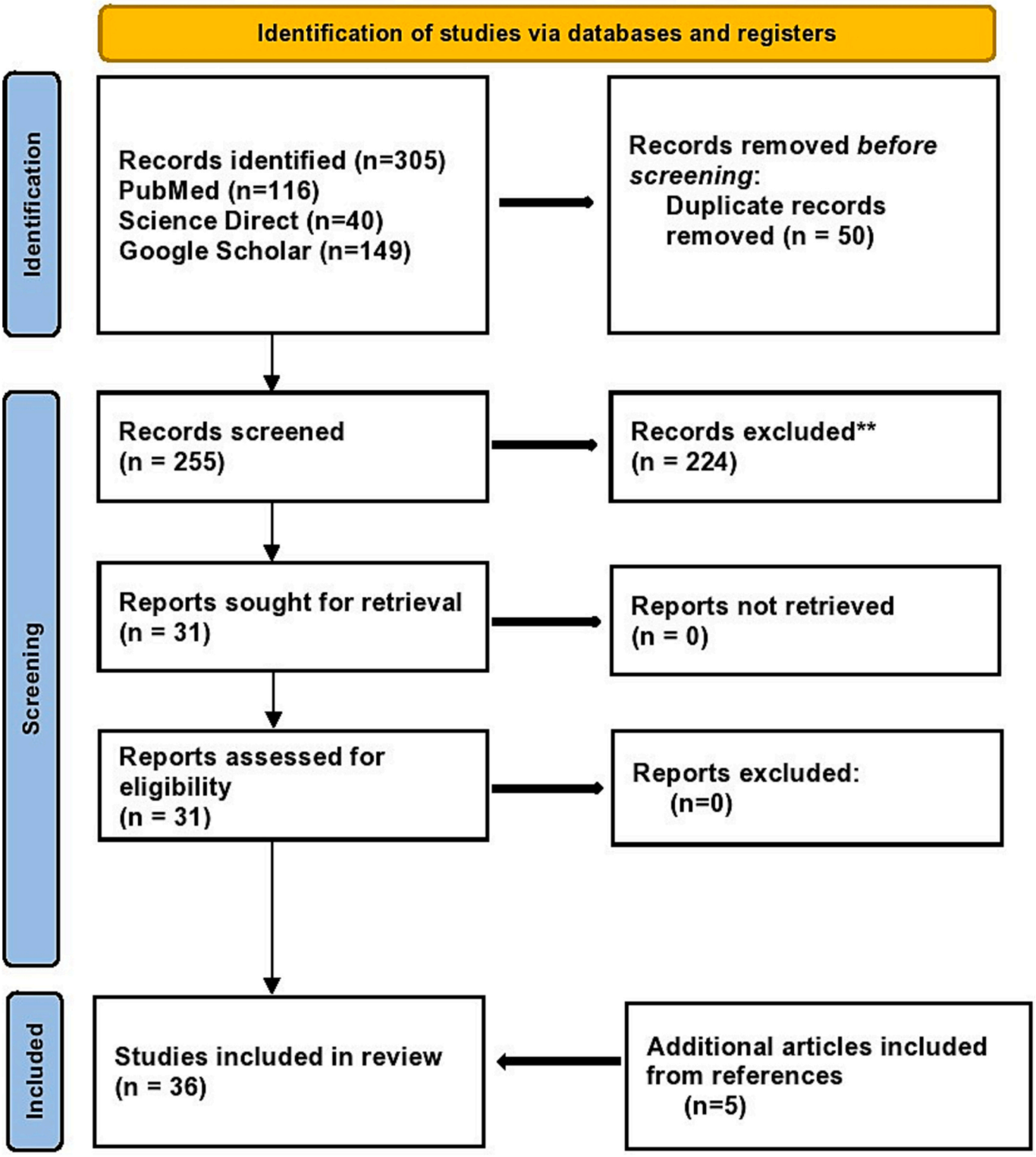

Fig. 1. PRISMA flow chart.

3.11. Microscopic examination

On microscopic examination, the tumor cells reportedly had an epithelioid appearance in 12/17 (70.6 %), and a spindled appearance in 5/14 (35.7 %); mitotic figures were found in 8/8 (100 %) and prominent nucleoli in tumor cells were specifically mentioned in 3/3 cases. A junctional melanocytic component was reportedly present in 13/21 (61.9 %) cases, absent in 8/21 (38.1 %) cases, and its presence or absence was not reported in 18/39 (46.2 %) cases.

3.12. Immunohistochemistry

Vimentin was positive in 8/8 (100 %) cases. It was not reported in 31/39 (79.5 %) cases. S-100 was positive in 11/11 (100 %) cases. It was

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Table 1
Summary of case reports of primary gallbladder melanoma.

Total sample size	Female ($n = 13$) 36 %	Male ($n = 23$) 64 %	Gender not mentioned (n = 3) 7 %	Total ($n = 39$) 100 %	Confidence interval (CI) [CI 95 %]	*P*-value [0.05]
Age (years)	56.5	54.5	48	55 ±16	48.3–58.8	0.023
Mean +/− SD						
Size of tumor (cm)	3.5 × 2 × 1.5 cm	3.4 × 1.9 × 1.3 cm	N/A	3.5 × 1.9 × 1.4 cm	46.8–61.8	0.31
Follow-up (months)	11.7	24.6	8.3	19 +/− 3	39.2–54.6	0.02
Mean +/-SD						
Ethnicity						
Caucasian	3/3 (100 %)	3/4 (75 %)	0/0 (0 %)	6/7 (85.7 %)	11.9–39.3	0.256
Japan	0/3 (0 %)	1/4 (25 %)	0/0 (0 %)	1/7 (14.3 %)		
Not reported	10/13 (76.9 %)	19/23 (82.6 %)	3/3 (100 %)	32/39 (82 %)		
Pigmented Lesion on Skin						
Yes						
No	2/11 (18.2 %)	4/18 (22.2 %)	0/1 (0 %)	6/30 (20 %)		
Not reported	9/11 (81.8 %)	14/18 (77.7 %)	1/1 (100 %)	24/30 (80 %)	9.9–36.3	0.231
	2/13 (15.3 %)	5/23 (21.7 %)	2/3 (66.6 %)	9/39 (23 %)		
Symptoms at Presentation						
Pain in Right Upper Quadrant						
Yes						
No	10/11(90.9 %)	9/15 (60 %)	1/1 (100 %)	20/27 (74 %)		
Not reported	1/11 (9.1 %)	6/15 (40 %)	0/1 (0 %)	7/27 (26 %)	18.5–48.1	0.33
	2/13 (15.4 %)	8/23 (34.8 %)	2/3 (66.6 %)	12/39 (30.7 %)		
Nausea/Vomiting						
Yes						
No	9/10 (90 %)	3/14 (21.4 %)	0/1 (0 %)	12/25 (48 %)		
Not reported	1/10 (10 %)	11/14 (78.6 %)	1/1 (100 %)	13/25 (52 %)	14.1–42.3	0.282
	3/13 (23 %)	9/23 (39.1 %)	2/3 (66.6 %)	14/39 (35.9 %)		
Gallbladder Calculi						
Yes	3/10 (30 %)	4/15 (26.6 %)	0/2 (0 %)	7/27 (26 %)		
No	7/10 (70 %)	11/15 (73.3 %)	2/2 (100 %)	20/27 (74 %)	20.8–51.0	0.359
Not reported	3/13 (23 %)	8/23 (34.8 %)	1/3 (33.3 %)	12/39 (30.7 %)		
Cholecystectomy						
Yes	13/13 (100 %)	19/23 (82.6 %)	2/2 (100 %)	34/38 (89.5 %)		
No	0/13 (0 %)	4/23 (17.4 %)	0/2 (0 %)	4/38 (10.5 %)	4.1–26.7	0.154
Not reported	0/13 (0 %)	0/23 (0 %)	1/3 (33.3 %)	1/39 (2.6 %)		
Gross findings						
Polypoid shaped						
Yes	12/12 (100 %)	15/16 (93.8 %)	1/1 (100 %)	28/29 (96.5 %)		
No	0/12 (0 %)	1/16 (6.3 %)	0/1 (0 %)	1/29 (3.5 %)	49.0–79.2	0.641
Not reported	1/13 (7.7 %)	7/23 (30.4 %)	2/3 (66.6 %)	10/39 (25.6 %)		
Papillary shaped						
Yes	1/12 (8.3 %)	2/10 (20 %)	0/1 (0 %)	3/23 (13 %)		
No	11/12 (91.6 %)	8/10 (80 %)	1/1 (100 %)	20/23 (87 %)	4.1–26.7	0.154
Not reported	1/13 (7.7 %)	13/23 (56.5 %)	2/3 (66.6 %)	16/39 (41 %)		
Microscopic examination						
Junctional Melanocytic Component						
Yes						
No						
Not reported	6/9 (66.6 %)	6/11 (54.5 %)	1/1 (100 %)	13/21 (61.9 %)		
Spindle Shaped cells	3/9 (33.3 %)	5/11 (45.5 %)	0/1 (0 %)	8/21 (38.1 %)	23.2–53.7	0.385
Yes	4/13 (30.7 %)	12/23 (52.2 %)	2/3 (66.6 %)	18/39 (46.2 %)		
No						
Not reported	2/5 (40 %)	3/9 (33.3 %)	0/0 (0 %)	5/14 (35.7 %)		
Epithelioid Shaped cells	3/5 (60 %)	6/9 (66.6 %)	0/0 (0 %)	9/14 (64.3 %)	35.6–67.0	0.513
Yes	8/13 (61.5 %)	14/23 (60.8 %)	3/3 (100 %)	25/39 (64.1 %)		
No						
Not reported	6/8 (75 %)	6/9 (66.6 %)	0/0 (0 %)	12/17 (70.6 %)		
Mitotic figures	2/8 (25 %)	3/9 (33.3 %)	0/0 (0 %)	5/17 (29.4 %)	92.6–100	1.00
Yes	5/13 (38.5 %)	14/23 (60.8 %)	3/3 (100 %)	22/39 (56.4 %)		
No						
Not reported	4/4 (100 %)	4/4 (100 %)	0/0 (0 %)	8/8 (100 %)		
Prominent nucleoli	0/4 (0 %)	0/4 (0 %)	0/0 (0 %)	0/8 (0 %)	57.7–85.9	0.718
Yes	9/13 (69.2 %)	19/23 (82.6 %)	3/3 (100 %)	31/39 (79.5 %)		
No						
Not reported	3/3 (100 %)	0/0 (0 %)	0/0 (0 %)	3/3 (100 %)		
	0/3 (0 %)	0/0 (0 %)	0/0 (0 %)	0/3 (0 %)	11.9–39.3	0.051
	10/13 (76.9 %)	23/23 (100 %)	3/3 (100 %)	36/39 (92.3 %)		
Immunohistochemistry						
Vimentin						
Positive	4/4 (100 %)	4/4 (100 %)	0/0 (0 %)	8/8 (100 %)		
Negative	0/4 (0 %)	0/4 (0 %)	0/0 (0 %)	0/8 (0 %)	49.0–79.2	0.417
Not reported	9/13 (69.2 %)	19/23 (82.6 %)	3/3 (100 %)	31/39 (79.5 %)		
S-100						
Positive	5/5 (100 %)	6/6 (100 %)	0/0 (0 %)	11/11 (100 %)		

(*continued on next page*)

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Table 1 (*continued*)

Total sample size	Female ($n = 13$) 36 %	Male ($n = 23$) 64 %	Gender not mentioned (n = 3) 7 %	Total ($n = 39$) 100 %	Confidence interval (CI) [CI 95 %]	*P*-value [0.05]
Negative	0/5 (0 %)	0/6 (0 %)	0/0 (0 %)	0/11 (0 %)	28.0–59.2	0.436
Not reported	8/13 (61.5 %)	17/23 (73.9 %)	3/3 (100 %)	28/39 (71.8 %)		
HMB-45						
Positive	7/7 (100 %)	4/4 (100 %)	1/1 (100 %)	12/12 (100 %)		
Negative	0/7 (0 %)	0/4 (0 %)	0/1 (0 %)	0/12 (0 %)	4.1–26.7	0.075
Not reported	6/13 (46.2 %)	19/23 (82.6 %)	2/3 (66.6 %)	27/39 (69.2 %)		
Metastases						
Yes	8/13 (61.5 %)	16/21 (76.2 %)	1/2 (50 %)	25/36 (69.4 %)		
At baseline	7/8 (87.5 %)	14/16 (87.5 %)	1/1 (100 %)	22/25 (88 %)	7.8–33.2	0.286
At follow-up	1/8 (12.5 %)	2/16 (12.5 %)	0/1 (100 %)	3/25 (12 %)		
No	5/13 (38.5 %)	5/21 (23.8 %)	1/2 (50 %)	11/36 (30.6 %)		
Not reported	0/13 (0 %)	2/23 (8.6 %)	1/3 (33.3 %)	3/39 (7.7 %)		
Patient Status						
Dead	7/12 (58.3 %)	9/18 (50 %)	1/3 (33.3 %)	17/33 (51.5 %)		
Alive	5/12 (41.6 %)	9/18 (50 %)	2/3 (66.6 %)	16/33 (48.5 %)	57.7–85.9	0.59
Not reported	1/13 (7.7 %)	5/23 (21.7 %)	0/3 (0 %)	6/39 (15.4 %)		

not reported in 28/39 (71.8 %) cases. HMB-45 was positive in 12/12 (100 %) cases. It was not reported in 27/39 (69.2 %) cases.

3.13. Metastasis

Metastasis was reported in 25/36 (69.4 %) cases. In 11/36 (30.6 %) cases it was absent. In 3/39 (7.7 %) cases it wasn't reported. Metastasis at baseline was reported in 22/25 (88 %) cases and at subsequent follow-up in 3/25 (12 %) cases. Majority of the cases 17/39 (43.6 %) reported Stage 4B at presentation. Lymph nodes were the most common site ($n = 8$), followed by brain ($n = 6$) and liver ($n = 4$).

3.14. Survival data

Survival data was found in 33 cases, with 16/33 (48.5 %) alive at follow-up, and 17/33 (51.5 %) having died because of complications of the disease. Survival data was not reported in 6/39 (15.4 %) cases.

4. Discussion

The incidence and prevalence of primary gallbladder melanoma cannot be predicted owing to its rarity; however, based on the findings of our review, it appears to be more prevalent in males (64 %) than in females (36 %). It has been reported in both younger and older populations, with a wide range of age distribution (29–80 years). Based on ethnicity, there is a predominance of the white population, but sporadic cases have been reported from Japan as well. On the basis of small size ($n = 39$), commenting on the preponderance of primary gallbladder melanoma to any specific gender, age, and ethnic group is early. Therefore, future cases labelled as primary gallbladder melanoma by pathologists should include age, sex, ethnicity, and most importantly, genetic studies of such individuals, so that our understanding of its etiology and predilection can be clarified.

Clinically, it is almost impossible to diagnose primary gallbladder melanoma as it mostly presents as acute cholecystitis with symptoms of pain in the right upper quadrant (74 %), followed by nausea and vomiting (48 %); therefore, the differential diagnosis has to be broad initially and further narrowing has to be done by radiological and pathological investigations. Physical examination is the most important part of any diagnosis in medical practice; however, pathologists agree that it is the most important step for diagnosing primary gallbladder melanoma. Thorough physical examination of the whole body sometimes reveals the primary focus of the melanoma. Physical examinations should include ocular and genital examinations. On physical examination, pigmented lesions other than those in the gallbladder were found in 6/30 (20 %) patients; however, such lesions were not present in the initial documentation. There is a concept of cutaneous melanoma regression in which melanoma can regress, and the secondary metastatic site of melanoma appears to be the primary source of melanoma. None the less whether the melanoma is primary or secondary metastatic to the gallbladder clinically does not have any significance, as the management of both is similar, that is, surgical excision and chemotherapy.

Primary gallbladder melanoma should be differentiated from adenocarcinoma of the gallbladder, which is far more prevalent than GB melanoma [40]. GB adenocarcinoma is more common in older women, whereas GB melanoma is more common in middle-aged men. Unlike melanoma, adenocarcinoma is associated with cholelithiasis. Small cell carcinoma, squamous cell carcinoma, carcinosarcoma, and lymphoma are relatively uncommon diagnosis [40]. Renal cell carcinoma can potentially spread to the bloodstream, whereas hepatocellular carcinoma is locally invasive. The differential diagnostic list also includes benign lesions such as cholesterol polyps, inflammatory polyps, adenomyomatosis, and adenomatous polyps [40,41].

Grossly, the tumor has polypoid shape prominently in 96.5 % of cases, with an average tumor size of 3.5 × 1.9 × 1.4 cm. The tumor is usually completely confined to the mucosa, with only limited invasion of the muscularis propria and subserosa [11]. Microscopically it is composed of mostly pigmented polygonal cells with vesicular nuclei, conspicuous eosinophilic nucleoli and mitotic figures. The tumor cells have epithelioid appearance (70.6 %) and sporadically spindle shaped cells (35.7 %). The lining of the villi of the gall bladder mucosa consists of tall columnar cells with pigmented neoplastic cells and macrophages in between [11]. Junctional activity, defined as the presence of microscopic aggregates of melanoma cells at the junction of the epithelium and lamina propria, is typically present (61.9 %) [11]. The tumor is extremely aggressive, and 70 % of cases usually spread to the liver and brain as shown in Table 1 and Results section. Tumor cells typically stain positive for S100, HMB45, Melan A, and CD117 by immunohistochemistry; however, histological characteristics and immunohistochemistry make it difficult to distinguish primary from metastatic lesions [11]. Mac Fadden et al. investigated primary and metastatic biliary melanomas and discovered notable pathologic similarities between the two groups [42]. According to the literature, the following clinical and pathological criteria should be met in order to differentiate between primary and metastatic gallbladder melanoma: (1) By medical history and laboratory analysis, any other obvious primary site must be ruled out; and (2) the tumor, whether papillary or polypoid, must be solitary, arise from the gallbladder mucosa, and have junctional activity [1,2,15]. Junctional activity, defined as intraepithelial expansion in the mucosa overlying a tumor, is regarded as a critical feature in the diagnosis of primary mucosal surface melanoma [1,42]. The presence of atypical melanocytes in the surrounding epithelium of an invasive tumor, on the other hand, does not always indicate a primary tumor [1]. Although the presence of "junctional changes" in the mucosa is still

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debated, the presence of a solitary polypoid tumor within the lumen of the gallbladder accompanied by junctional activity within the tumor, as well as the absence of an antecedent history of melanoma or the absence of another obvious primary site, are factors that point to the gallbladder as the primary site of origin. Finally, even today, establishing primary histogenesis in these individuals requires a complete medical history, thorough cutaneous and ocular examination, and radiologic control [1]. There is always a possibility that a regressed primary tumor is the cause of gallbladder melanoma. In terms of clinical presentation, gallbladder involvement rarely causes symptoms, which could explain the paucity of cases reported in the literature [1], and is usually reported as a case of acute cholecystitis without the presence of stones as the initial clinical manifestation and the reason for emergency admission in the hospital in the majority of cases. All these criteria for separating primary from secondary malignant melanoma of the gallbladder are inadequate, especially when viewed individually. Metastatic melanoma can take the shape of a polypoid pattern [43], a single tumor mass [13,42], intraepithelial dissemination and junctional activity, or a single metastatic site [44-46]. Guidelines for determining the diagnosis of this primary entity are based on the clear presence of specific characteristics [15].

Unlike gallbladder cancer, melanomas of the gallbladder do not appear to be associated with cholelithiasis. In our review, only 26 % of reported individuals had intermittent gallstones. After reviewing the literature, Dong et al. discovered that gallstones appear to be only incidentally present in 21.1 % of cases (4 of 19 patients) with primary lesions and 27.3 % of cases (3 of 11 patients) with symptomatic metastatic disease, which is consistent with the results of their series [13]. Several diagnostic methods have been used to investigate gallbladder lesions. The most useful instrument in this endeavor is the ultrasound. Upper abdominal ultrasonography tests are routinely performed in individuals with dense, high-grade melanoma or clinical suspicion of metastases. Metastatic lesions within the gallbladder can be detected using ultrasound. Polypoid lesions in the gallbladder lumen, on the other hand, cause focal thickening of the gallbladder wall without acoustic shadowing due to their lower density compared to gallstones. Autopsy studies have revealed a 15 % incidence of gallbladder metastasis from malignant melanoma, and a comprehensive assessment of the gallbladder is advised when performing an abdominal ultrasound examination in a patient with malignant melanoma. Ultrasonography can assist in differentiating between metastatic and benign polyps. The significance of lesion size is clear, as 94 % of benign lesions are <1 cm in diameter, whereas 88 % of malignant lesions are >1 cm [47]. The utility of color-flow doppler ultrasonography is obvious if vascular flow within the bulk is confirmed [48]. Computed tomography (CT) has some utility, particularly for detecting metastatic illnesses [1].

Surgical excision is the preferred treatment for both primary and metastatic gallbladder melanomas. A comprehensive search is required during surgery to identify any probable abdominal metastases, as the majority of gallbladder metastases are completely asymptomatic. Although most metastases take the form of multiple serosal implants, intraluminal metastases affect the mucosa, which makes finding these metastases after surgery difficult. Although surgical removal of the gallbladder is the cornerstone of treatment, further research into the function of adjuvant chemotherapy, hormone therapy, and immunotherapy in enhancing survival is required [7]. The occurrence of several metastases indicates the need for thorough chemotherapy. Only one controlled experiment has indicated a substantial improvement in response rate and mid survival with the combination of dacarbazine and tamoxifen [49]; therefore, the utility of adjuvant chemotherapy for both primary and metastatic melanomas remains unknown. Adjuvant treatment is debatable. Adjuvant local postoperative radiation therapy with approximately 60, 66, and 70 Gy was customarily fractioned for R0, R1, and R2 resection, which is generally used for other primary mucosal melanomas. However, its function in the gallbladder remains unclear [7]. This may improve local control when widely clear margins are not feasible [50]. Selected patients with mucosal melanomas (cases with thick mucosal lesions involving or not involving lymph nodes) can be exposed to postoperative interferon therapy trials; however, the response has not been proven. Therefore, these patients may also be eligible for adjuvant clinical trials [51]. The key management decision point in advanced melanomas is the determination of the BRAF mutational status. Only patients expressing mutant BRAF at position V600 have been approved for therapy with BRAF and MEK inhibitors. Preclinical studies have shown that BRAF inhibitors are not only ineffective in patients who do not have the BRAF V600 mutation, but are also harmful to patients by activating the MAPK pathway and increasing cancer progression [52-55]. New effective systemic therapies [56], including CTLA-4 blockers, PD-1 blockers, and BRAF/MEK inhibitors, may be options for patients with tumors that are too large to resect. However, multidisciplinary team evaluation is recommended to balance the short-term danger of postponing surgery against the possibility of considerable systemic tumor regression with these medicines. Adaptive cell treatments have recently gained popularity. It is a type of immunotherapy in which anticancer activity is pumped into tumor-bearing cells, resulting in the detection of tumor antigens and destruction of cancer cells. When treated with adaptive cell therapy, 50–70 % of patients with metastatic melanoma have objective cancer regression, as measured by the Response Evaluation Criteria in Solid Tumors [57,58].

For melanoma follow-up, the German S3 guidelines [59] or National Comprehensive Cancer Network (NCCN) V3.2020 guidelines [60] might be employed. Because primary melanoma of the gallbladder is more aggressive than metastatic melanoma of the gallbladder, doctors may select criteria for stage IV illness. The prognosis for both primary gallbladder melanoma and metastatic gallbladder melanoma is poor [7]. As demonstrated in Fig. 2 (Kaplan–Meier curve), 51.5 % of the patients in our review died after an average follow-up of 19 $+/-$ 3 months. The mortality rate in females was slightly higher (58.3 %) than that in males (50 %), indicating that surgical excision via cholecystectomy and current chemotherapy are not curative.

5. Limitations

The current systematic review has limitations; to date, only case reports/case series related to primary gallbladder melanoma are available. There is a dearth of large-scale observational studies that provide authentic data. Case reports by design lack internal validity, and any conclusions drawn from them need to be verified by observational studies and clinical trials, which was certainly not possible with only the sample size ($n = 39$). The small sample size and significant heterogeneity among patient data significantly reduced the power of our analysis. Second, the cases were selected only in English literature with full-text availability; therefore, articles in other languages with significant findings would have been skipped. Third, the ethnicity and genetic analysis of the patients was missing from the majority of the case

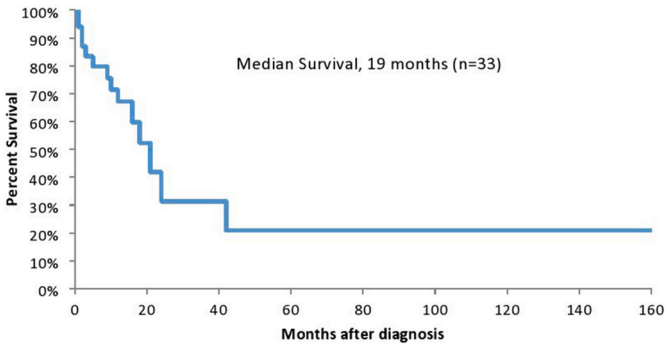

Fig. 2. Overall survival of primary gallbladder melanoma. Kaplan–Meier curve shows that the patients with Primary gallbladder melanoma had a median survival of 19 months ($n = 33$).

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reports. It is important to mention the ethnicity and genetic prevalence of the patients because it helps to evaluate the prevalence of the disease in a particular population. It also helps in tailoring treatment. Therefore, future studies should include complete demographic and genetic characteristics.

6. Conclusions

Our review summarizes the available case reports/case series. The primary gallbladder melanoma is a highly aggressive tumor with a high mortality risk. Clinically, it presents as acute cholecystitis, and for definitive diagnosis, histopathology, and immunohistochemistry, thorough investigation of the primary source of melanoma is essential. The current treatment strategy involves surgical resection along with chemotherapy. There is a lack of unified criteria for its diagnosis; hence, it has not been classified. Therefore, future studies should aim to resolve this.

Authors contribution

All authors contributed equally in drafting this manuscript.

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CRediT authorship contribution statement

Shafi Rehman: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Pravallika Venna:** Writing – review & editing, Writing – original draft, Data curation. **Sissmol Davis:** Writing – review & editing, Writing – original draft, Data curation. **Ragini Gopagoni:** Writing – review & editing, Writing – original draft, Data curation. **Ritika Uttam:** Writing – review & editing, Writing – original draft, Data curation. **Ameer Mustafa Farrukh:** Writing – review & editing, Writing – original draft, Data curation. **Mahsa Salehi:** Writing – review & editing, Writing – original draft, Validation, Supervision.

Declaration of competing interest

None.

Data availability

Data is available on request.

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