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Gallbladder GIST: A review of literature

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ABSTRACT: Mesenchymal tumors of the gallbladder are rarely encountered in clinical practice. The Gastrointestinal Stromal Tumor (GIST) of the gallbladder is rarely encountered. These tumors most commonly arise from the interstitial cells of Cajal (ICC), the pacemakers of the intestinal system. There can be benign as well as malignant forms of GIST. The literature on GIST arising from the gallbladder wall is limited to a few case reports only. In extensive search of the indexed literature, only 9 cases of gallbladder GIST were retrieved. Based on the available literature these tumors are commonly found in females. They usually present with hypochondrial pain with or without other features of cholangitis. These tumors are usually malignant and warrant a radical surgical excision. The data on postoperative adjuvant therapy and survival is limited. The authors presented a review of the available literature on this rare pathology.

KEYWORDS: gallbladder, GIST, interstitial cells of cajal

ABBREVIATIONS

CBD – common bile duct
GI – gastrointestinal
GIST – gastointestinal stromal tumors
ICC – interstitial cells of cajal
IHC – immunohistochemical tests
NIH – National Institute of Health
RHC – Right Hypochondrial

INTRODUCTION

Tumors arising from the mesenchymal tissue of the gallbladder are rarely encountered in clinical practice. Various histological types like leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, and Kaposi sarcoma have been reported in the English literature [1]. Gastrointestinal stromal tumor (GIST) arising from interstitial cells of Cajal (ICC) is the most common one among all the mesenchymal tumors of the gastrointestinal system [2]. These cells are responsible for pacemaker activity of the gastrointestinal system [3]. GISTs most commonly arise from the stomach followed by small intestine [4]. However, they can arise from any part of the gastrointestinal (GI) tract starting from the esophagus to rectum. These cells are present in the subepithelial and muscular layer of the gallbladder [5]. The gallbladder GIST was first reported by Ortiz-Hidalgo C. et al. in 2000 [6]. Since then, only 9 such cases have been reported in the indexed literature [4, 6–13]. These tumors may mimic multiple benign pathologies affecting the gallbladder [14]. A review of literature regarding this rare entity is essentially lacking. Herewith the authors made an attempt to provide an insight into the development, pathogenesis, clinical features, histology and treatment of the pathology from available literature.

DEVELOPMENT OF GALL BLADDER

The hepatic diverticulum arises from the ventral wall of the primitive midgut. It arises in the fourth week of intrauterine life [15]. This bud is differentiated into two parts [16]. The cranial one gives rise to the liver and extrahepatic biliary system whereas the caudal one gives rise to the gallbladder, cystic duct and pancreas. The gallbladder precisely arises from the superior part of the caudal hepatic diverticulum [16–17]. All the parts of the biliary system are recognizable by the fifth week of intrauterine life [16]. The recanalization of the biliary system starts at the end of the fifth week and the cystic duct is canalized by the seventh week of life [17]. Gallbladder however remains solid and recanalizes at 12 weeks [18]. From the common development of the gallbladder and the gastrointestinal system it can be postulated that the tumors of the GI system can arise de novo from the hepatobiliary system as well.

The occurrence of the GIST from the gallbladder can be proved by the presence of ICC-type cells in the gallbladder. Hinescu M.E. et al. [5] in their study demonstrated the presence of ICC in a human gallbladder specimen. They were present in the specimen with a spatial density of 100–110 cells/mm^2 and were confirmed with relative immunohistochemistry. According to the authors, these cells constituted around 5.5% of all subepithelial cells. They were concentrated in the subepithelial and the muscular tissue of the gallbladder. Hence, from this study it can be postulated that tumors arising from these cells will be subepithelial in nature. Contrary to this study, Parr E.J. et al. [19] failed to demonstrate any ICC in the gallbladder. This study was conducted on guinea pigs and is less relevant in human context as a study on human tissue has already been published.

PATHOGENESIS

Mutation of c-kit is present in 70–80% of GISTs. This mutation is the inciting factor in most of the GIST cases [20]. These genes encode a tyrosine kinase receptor and their mutation phosphorylates various proteins, leading to the activation of signal transduction cascades regulating cell proliferation, apoptosis, chemotaxis, and adhesion. Kit mutations are present on exon 9, 11, 13, and 17. Most of these mutations are heterozygous [21]. Although the mutation in c-kit is the primary inciting event, multiple secondary mutations are required for the development of an aggressive GIST [22]. Although c-kit is proposed to be the major inciting factor in the development of GIST. PDGFRA mutations are found in 7–17% of GISTs. This gene is present along with kit on chromosome 4q. These genes are mutually exclusive and drive the pathogenesis in the same pathway [23].

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Tab. I. Table showing the demographic, clinical features and surgical management of the reported cases.

Park et al. [4]	72 years	Female	Right hypochondrial (RHC) pain with fever	cholecystectomy
Hidalgo et al. [6]	69 years	Female	RHC pain	Laparoscopic cholecystectomy
Marin et al. [7]	34 years	Female	RHC pain	Cholecystectomy followed by wedge resection
Peerlinck et al. [8]	79 years	Female	RHC pain with fever	Simple cholecystectomy
Bolanki et al. [9]	77 years	Female	Cholangitis	Metastatic GIST
Furihata et al. [10]	68 years	Female	RHC pain with mass	Extended right hepatectomy with hepaticojejunostomy after Portal vein embolization
Petrou et al. [11]	72 years	Female	Cholangitis with hilar block	Radical cholecystectomy with CBD excision and hepaticojejunostomy
Daraji et al. [12]	48 years	Female	Pain with fever	Simple cholecystectomy
Daraji et al. [13]	88 years	Female	Pain jaundice and fever	NA

Tab. II. Table showing the histopathological characteristics of the tumors.

	SIZE	MASS OR THICKENING	MORPHOLOGY	WSKAŹNIK MITOTYCZNY	CD117	CD 34/OTHERS IF POSITIVE
Park et al. [4]	6 × 3 cm	Mass	Spindle shaped	>20/50	Positive	Negative
Hidalgo et al. [6]	2 × 2 cm	Mass	Spindle shaped	Na	Positive	Positive
Marin et al. [7]	1,5 cm	Mass	Spindle shaped	>28/10	Positive	Negative
Peerlinck et al. [8]	4 cm	Mass	Spindle shaped	>90%	Positive	Desmin-positive
Bolanki et al. [9]	>5 cm	Mass	Spindle shaped	>50/50	Positive	Negative
Furihata et al. [10]	6 × 5 × 4 cm	Mass	Spindle shaped	>5/10	Positive	Negative
Petrou et al. [11]	7,5 × 3,5 cm	Mass	Spindle shaped	>50/50	Negative	PDGFRA-positive
Daraji et al. [12]	2 × 1 cm	Mass	Spindle shaped	<1/50	Positive	Negative
Daraji et al. [13]	Absent	Mass	GIST-like	Na	Negative	Negative

Non-mutated ckit and PDGFRA GISTs are also reported. These are called wild GISTs and most of them consist of BRAF mutation. Mutation in succinate dehydrogenase has also been implicated in a few GISTs [24]. All these are the primary inciting factors for the development of these tumors. Secondary mutations like deletions of 1p, 9p, 11p, 14q, 22 and gains of 8p and 17q also add to the aggressiveness and increased malignant potential of these tumors [25].

CLINICAL FEATURES

GIST was first reported as an incidental finding. It was present as a nodule in the wall of the gallbladder removed for chronic cholecystitis [6]. To date, 6 cases of malignant GIST are reported in literature. As the gallbladder diseases are more common in females these tumors have been reported more commonly in them. Various presentations of gallbladder GIST have been reported in literature. It varies from an incidental benign tumor [6] to an aggressive metastatic tumor [4]. A report of GIST along with obstructed jaundice secondary to hilar block was reported by Petrou A. et al. [11] Hence the preoperative suspicion of gallbladder GIST is difficult as gallbladder adenocarcinoma is more commonly encountered in clinical practice.

DIAGNOSIS

The gallbladder GIST presents as asymmetrical mural thickening of the gallbladder wall [4]. It is usually an incidental finding on histopathological evaluation [6]. Contrast-enhanced CT scan of the abdomen will reveal asymmetrical thickening of the gallbladder. The lymph node mass may characteristically be absent in adults as these tumors metastasize through hematogenous and peritoneal routes [26].

The histopathology typically reveals spindled to oval epithelioid cells arranged in short fascicles [6]. These cells may sometimes be confused with leiomyoma or other mesenchymal tumors [7]. Till the advent of the immunohistochemical (IHC) tests these tumors were falsely reported as undifferentiated carcinoma or sarcomatoid squamous cell carcinoma [1]. The immunohistochemistry for squamous cell carcinoma will be positive for cytokeratin whereas the melanoma can be positive for CD117, HMB45, and S100 [7].

The spindle-shaped cells of the GIST typically stain positive for kit and CD 34 mutations [27]. This was found by Lasota et al. [27] whose work has definitely demonstrated the kit and CD34 positivity in the GIST cells. The immunohistochemistry for these stains helps the pathologists to differentiate these tumors from other benign or malignant mesenchymal tumors. The detection of these mutations in the gallbladder mass predicts the sensitivity of these tumors to adjuvant tyrosine kinase inhibitors like imatinib [28]. The wild types of GIST are essentially resistant to tyrosine kinase inhibitors and are candidates for the second line of therapy [11]. The kit-negative tumors are aggressive and possess dismal prognosis. Immunohistochemical staining for DOG1 can also help to diagnose a kit-negative GIST [29].

The natural progression of the GIST can be predicted by the size of the tumor and the number of mitosis per 50 high power fields [11]. This work was initially proposed in the NIH guidelines and mul-

tiple modifications have been made since then [27]. Presence of a large tumor along with a high mitotic index makes the patient a candidate for the adjuvant tyrosine kinase blockers.

All the malignant cases of gallbladder GIST are kit-positive except for one reported by Petrou A. et al. [11] The tumor was kit-negative but was positive for PDGFRA. This was the first ever case of gallbladder GIST with this IHC profile.

TREATMENT

The gallbladder GIST is essentially a histopathological surprise [6]. Cholecystectomy may suffice for a small benign tumor. The patients are usually diagnosed as gallbladder adenocarcinoma and treated accordingly. The radical cholecystectomy including removal of segment 4b/5 of the liver along with standard lymphadenectomy should be done whenever a more aggressive carcinoma is suspected [11]. However, the role of lymphadenectomy is controversial provided the preoperative diagnosis of gallbladder GIST is known. As these tumors involve the lymphatics less commonly (6%) the operating surgeon should concentrate more on the negative margins of resection [30]. The wedge of the liver can always be removed as the malignant tumor might directly involve the adjacent liver. The presence of hilar block with GIST mandates the removal of the extrahepatic biliary system along with reconstruction of the biliary system with Roux-en-y hepaticojejunostomy [11]. The confirmation of the high malignant potential of the resected tumors mandates adjuvant therapy with imatinib [28]. The second-line therapy in the form of sunitinib and sorafenib can also be prescribed in imatinib-resistant cases [31].

PROGNOSIS

The five-year survival rate for GIST is reported to be around 46–78% [32]. However, these results cannot be duplicated to the gallbladder as the follow-up of these patients is essentially lacking.

In a report by Park J.K. et al. [4] the patient died after 9 months of therapy secondary to aggressive liver metastasis. The consensus on the follow-up and protocols for recurrent disease can only be framed once a large long-term follow-up is available.

CONCLUSION

The gallbladder GIST is a rare mesenchymal tumor. It is essentially a histopathological diagnosis. Strong positivity for CD 117 helps to differentiate these tumors from other mesenchymal tumors. Radical surgery along with adjuvant chemotherapy offers a chance for a long-term survival. Long-term follow-up is required to frame the policies for patient follow-up as well as recurrence.

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