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Gallbladder complications associated with molecular targeted therapies: clinical and imaging features

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ABSTRACT

Objectives: To evaluate the clinical and imaging features of molecular target therapies (MTT)-associated gallbladder complications. **Methods:** The clinical presentation, imaging features, management, and outcome in six consecutive patients, who developed gallbladder complications while on monotherapy with MTT, were studied. **Results:** Imaging features included gallbladder distension, edema, hyperemia, pericholecystic fluid, and stranding. Two of the six patients were asymptomatic and continued the drug due to good response. Four of the six patients developed acute cholecystitis and required drug discontinuation temporarily or permanently with 2/4 patients requiring surgery. **Conclusion:** MTT can be associated with gallbladder complications that may need temporary or permanent discontinuation of the associated drug.

1. Introduction

There has been a paradigm shift in cancer care with the development of targeted therapies that act at a molecular level with high specificity for cancer cells. Several of these drugs are U.S. Food and Drug Administration-approved and are now an integral part of the management of certain cancers such as breast cancer, renal cell carcinoma (RCC), colon cancer, gastrointestinal stromal tumor (GIST), and leukemia, to name a few. These targeted agents have a good safety profile; nevertheless, toxicities, some life-threatening, are known to occur. Concurrent with the emergence of molecular targeted therapies (MTTs), there has been increasing awareness of associated complications. Common gastrointestinal side effects of MTT include nausea, vomiting, diarrhea, mucositis, abdominal pain, asymptomatic elevation of liver function tests (LFT), and pancreatic enzymes [1,2]. Abdominal pain occurring in this subset of patients is nonspecific but can be a manifestation of more serious complications like hepatitis, pancreatitis, cholecystitis or bowel-related complications [3–5]. These complications warrant prompt detection and cessation or modification of the MTT. Drugs that have a reported association with these complications include antivascular endothelial growth factor antibodies like bevacizumab, tyrosine kinase inhibitors like sunitinib and sorafenib, and mammalian target of rapamycin (m-TOR) inhibitors like everolimus.

Imaging plays a pivotal role in the monitoring of patients on MTT by not only assessing treatment response but also detecting complications at the right time. Acute cholecystitis as a complication of MTT has been described in isolated case reports and observed in large studies evaluating new drugs [6–11]. Though radiologists are familiar with the imaging features of cholecystitis, its occurrence and clinical impact in the context of MTT are not widely known to the radiology community. The literature on the consequences of detecting changes in gallbladder (GB) is also scant. In this study, we report six consecutive patients with GB complications while receiving novel MTT at our tertiary cancer center and evaluate the clinical and imaging features.

2. Materials and methods

This is a Health Insurance Portability and Accountability Act-compliant retrospective study, which was approved by the institutional review board with waiver for informed consent. The study subjects were identified through search of the radiology database from January 2005 to September 2012 for reports that mentioned GB complications (acute cholecystitis, GB edema, and GB sludge). The search yielded a total of 162 patients of which 6 patients who were receiving monotherapy with MTT at the time of the detection of GB complications were included in the study (Fig. 1). None of these patients were on concurrent chemotherapeutic drugs or known to have GB-related diseases including gallstones prior to start of the MTT.

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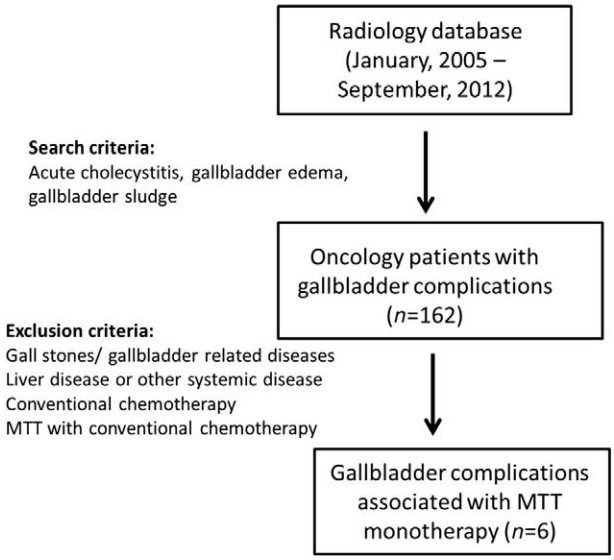

Fig. 1. Flow-chart depicting the patient selection and exclusion criteria.

None of the patient had comorbid conditions like diabetes, hypertension, liver disease, past history of cerebrovascular accidents, or ischemic heart disease. The imaging of all these six patients including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) was reviewed by two oncoradiology fellowship-trained radiologists with 8 and 14 years of experience in consensus. The imaging was reviewed to look for changes in GB like distension, sludge, stones, wall thickening, hyperemia, and pericholecystic fluid. The type of response of the underlying malignancy to the MTT at the time of detection of the GB complication was noted. The subsequent scans were reviewed to document the resolution of the complication, reappearance on rechallenge of the MTT, and the status of the malignancy.

The electronic medical records of all the six patients were reviewed to document the clinical features at the time of detection of the GB complication, laboratory investigations including hematology workup, LFT, the type of MTT, duration of treatment prior to the detection of the complication, and the management of the complication. A note was made if the MTT was discontinued and if discontinued, whether it was rechallenged [12].

3. Results

The clinical, biochemical and radiological findings, the management, and the eventual outcome are summarized in Table 1.

3.1. Clinical features and laboratory workup

There were five female patients and one male patient in the series, with age range of 38–73 years (Table 1). Two patients were on sunitinib, two on bevacizumab, and one each on everolimus and sorafenib at the time of presentation. The duration of the MTT prior to the detection of GB complications was variable, between 2 weeks and 5 months. Two of the six patients (33%) were asymptomatic and incidentally discovered to have GB edema and pericholecystic fluid on routine restaging scans. Of the two patients, one patient had elevated LFT [elevated aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (T-bil)], which waxed and waned for several years during the follow up, while the other patient had normal LFT. Four of the six patients (67%) had acute presentation clinically with right upper quadrant abdominal pain, fever, nausea, and vomiting. LFT were elevated in all of these patients [elevated AST: $n=2$, elevated alanine aminotransferase (ALT): $n=1$, elevated ALP: $n=2$, and

Table 1
Summary of the clinical and imaging features of molecular targeted therapy associated GB complications

No	Sex/ Age	MTT	Interval from the start of MTT to detection of GB complication (days)	Clinical symptoms	LFT (AST/ALT/ ALP/T-bil)*	Radiologic findings	Initial management	Follow-up	Response of the underlying disease†
1	f/73	Sorafenib	47	Asymptomatic	19/15/103/0.9	CT: GB wall edema US: Thickened edematous GB wall	Sorafenib continued	Follow-up CT in 1 month showed complete resolution of the abnormality	PR
2	f/71	Sunitinb	60	Asymptomatic	46/29/239/1.3	CT: Thickened, hyperemic GB wall, pericholecystic fluid US: Thickened edematous GB wall with pericholecystic fluid	Sunitinib continued	Persistent GB wall edema and pericholecystic fluid on CT for 4 years	PR
3	m/ 65	Sunitinib	13	Fever, nausea, abdominal pain	34/44/72/1.8	US: GB sludge MRI: GB sludge	Antibiotics, sunitinib stopped for 2 weeks	Sunitinib rechallenge resulted in recurrence of cholecystitis, cholecystostomy followed by cholecystectomy in 5 months	PR
4	f/68	Bevacizumab	80	Abdominal pain	42/64/112/0.4	CT: GB distension, dilated intrahepatic biliary radicles US: GB wall edema, sludge, dyskinetic GB	Antibiotics, bevacizumab discontinued transiently	Dose of bevacizumab was reduced, follow-up US 2 months later showed normal GB	SD
5	f/38	Bevacizumab	15	Nausea, vomiting	38/40/86/1.3	CT: GB wall edema, small amount of free air US: Thickened hyperemic GB wall	Antibiotics, bevacizumab discontinued permanently	Two follow up CT scans showed resolution	PD
6	f/69	Everolimus	140	Fever, nausea	29/15/246/0.7	CT: Distended GB, wall edema, pericholecystic stranding US: Thickened GB wall, hyperemia, gall stones HIDA: Acute cholecystitis	Antibiotics, everolimus discontinued permanently	Interval cholecystectomy 2 months later	PD

Foot notes: MTT: molecular targeted therapy; US: ultrasonography; PR: partial response; f: female; m: male.
* Normal range: AST: 9–30 U/L; ALT: 7–52 U/L; ALP: 36–118 U/L; T-bil: 0.2–1.2 mg/dl.
† Criteria: Response Evaluation Criteria in Solid Tumors ver.1.1/World Health Organization Criteria.