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RESEARCH ARTICLE

Tuberculosis and Cancer Gallbladder in Endemic Zones: Diagnostic and Surgical Dilemma for the Physicians

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ABSTRACT
Tuberculosis is an infectious disease widely prevelant in the developing world. The resurgence of tuberculosis is on rise even in the developed world as the chemotherapy and steroid use is increasing. Indo gangetic belt is endemic for both the tuberculosis and gallbladder cancer. Gallbladder cancer although rare pathology carries a high rate of morbidity and mortality.
Involvement of gallbladder in tubercular infection is rare. However, when involved there is a significant overlap of the clinical and radiological signs in both these patients. The treating physicians in these areas are always in therapeutic dilemma for the management of these patients. The other benign gallbladder pathologies mimicking the cancer further add on to the challenge in these patients. This article embarks upon the various challenges that a surgeon encounters in the management of these patients.

Keywords: Gallbladder tuberculosis, Thick-walled GB, Xanthogranulomatous gallbladder

Introduction:

Tuberculosis (TB) is an infectious disease affecting the majority of population in the developing world [1]. The infection leads to varied presentations depending upon the organ system involved. Essentially every organ in the human body is prone for TB infection. The clinical manifestations of the disease also depends upon the immunogenic resistance of the human body and as well as the resistance of the infecting organism to the conventional antitubercular drugs. The resurgence in TB is also being noted in the developed world where the immunocompromized patients increasing due to increased usage of corticosteroids, chemotherapy and HIV infections[2]. The tuberculosis in these patients is resistant to drugs and new chemotherapy is being tried for treatment of these patients.

Gall bladder cancers (GBC) is a dreadful malignancy seen in the countries like India, Pakistan and Bangladesh along the indo gangetic belt [3]. The malignancy usually presents at an advanced stage and is incurable at the initial presentation. Co existence of TB and GBC in these areas pose a diagnostic as well as therapeutic dilemma to the treating physicians[4].

There is a significant overlap of the symptoms and signs in patients suffering from benign and malignant gall bladder pathologies [4]. The significant overlap of the signs and symptoms challenges the treating consultants so as to decide on the further course of action. As these diseases are rare, the literature and guidelines for the management of these patients is not generalized.

Treatment of the patients on the line of malignancy is considered a safe strategy. However, these patients may be subjected to a morbid treatment for an otherwise benign and curable disease. The morbidity associated with extended cholecystectomy has been predicted in the range of 25-35%. The challenges encountered and the possible remedy to these challenges is the important focus of this manuscript.

Pathogenesis of the diseases:

Pathogenesis of TB abdomen is a well known process. Population living in the endemic areas of the globe gets infected during the early part of their life. The immune status of the body further decides about the course of disease in these individuals. The bacteria involves the respiratory system most commonly which is followed by the abdomen. The abdomen is involved after the host ingests the milk or saliva infected by mycobacterium tuberculosis or mycobacterium bovis. The bacteria resides in the lymphoid tissues and gets systemic access through the portal circulation [5]. The involvement of the various tissues of the abdomen leads to the presentation of tubercular abdomen (Fig 1).

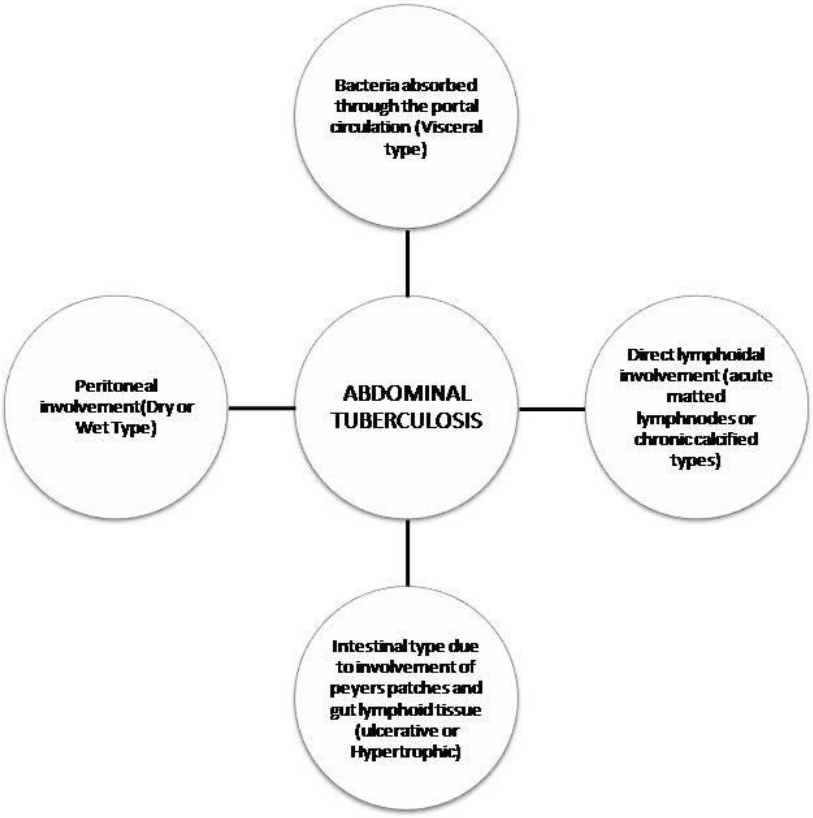

Figure 1: Figure showing various modes of Involvement in Abdominal tuberculosis

The gall bladder is rarely involved in TB infection. Alkaline nature of the biliary fluid and the inherent resistance of the GB mucosa protect it from the granulomatous inflammation. The GB is involved as a part of the miliary process, the infiltration of the serosa in the peritoneal involvement, rupture of the tubercular lymphnode and through the hematogenous and portal venous route[6].

Gallbladder cancer is caused by dysplasia and the metaplasia sequence secondary to the friction caused by the large stones. Prolonged inflammation cause the metaplasia and dysplasia of GB epithelium which turns malignant in due course of time [7].

Presence of chronic inflammation with superadded stressors that enhance cellular proliferation and DNA mutations lead to the formation of cancers. The gallbladder is unique as it lacks submucosa. The malignant cells directly infiltrate the muscular layer and the patient has advanced disease at the initial presentation.

Clinical features:

Tuberculosis of the GB presents as thickening of the GB wall along with the associated features. These features may be evening rise of temperature, loss of weight, loss of apetite, presence of multiple swellings in the neck and chronic cough [8]. History of contact with a positive patient may be elicited but it's rarely universal. The involvement of respiratory system will cause chronic cough and associated dyspnoea and hemoptysis depending upon the extent of the parenchymal involvement. Concomitant pulmonary and abdominal TB may present as abdominal pain, distention, Loss of weight and apetite along with the already described pulmonary symptoms.

GBC presents as pain in the right hypochondrium region which may radiate to the back. It presents like the typical gall stone pain with waxing and waning presentation [9]. However, the patients with GBC have change in the character of pain and may present with continuous dull aching pain. The other symptoms associated with GBC can be presence of features of obstructive jaundice like pruritis, clay coloured stools with high coloured

urine. The presence of cholangitis may cause fever with chills and rigors. These patients may present with shock and multi organ dysfunction in case of late presentation of cholangitis. Advanced cases of malignancy may also show signs of metastasis like Virchow's node and blummers shelf on the rectal examination.

There is a significant overlap in the symptoms of GBC and TB gallbladder [10]. However, there are multiple benign pathologies in the endemic zone of the gallbladder disease which mimics like malignant pathology. The various pathologies commonly encountered in the clinical practice in these areas are enumerated in table 1.

Table 1: Table showing various pathologies mimicking the GBC.

S.No	Pathologies Mimicking the GBC
1	Xanthogranulomatous Cholecystitis
2	Gall bladder Tuberculosis
3	Gallbladder polyps
4	IGG4 related cholecystitis
5	Porcelain gallbladder
6	Mucocele of the Gallbladder
7	Gallbladder Gastrointestinal stromal tumor
8	Vascular malformations in the Gall bladder
9	Other mesenchymal tumors like lipoma, liposarcoma, rhabdomyosarcoma etc

The presentations of the various pathologies with their advised treatment strategies have been demonstrated in table 2.

Table 2: Table showing various pathologies mimicking GBC and their treatment.

Pathology	Features and pathology	Treatment advised
Xanthogranulomatous Cholecystitis	Occurs due to rupture of Rockitansky Aschoff Sinuses and further inflammation of the GB wall. Presents as thick-walled GB and associated lymphadenopathy may be present[4]	Simple cholecystectomy
Gall bladder Tuberculosis	thick-walled GB along with peri portal and aortocaval lymphnodes[11]	Anti tubercular Chemotherapy
Gallbladder polyps	May be solitary or multiple, sessile or pedunculated, presents as mass in the gallbladder with wall thickening	Single, sessile polyp more than 10mm requires cholecystectomy whereas multiple GB polyps can be observed.
IGG4 related cholecystitis	Present as thick-walled GB along with involvement of other exocrine gland involvement[12]	Steroids and immunosuppressant.
Porcelain gallbladder	thick-walled calcified gallbladder	Simple cholecystectomy
Mucocele of the Gallbladder	Thicked GB wall with stone impacted in the neck. There may be associated periportal lymphadenopathy which is usually insignificant	Simple cholecystectomy
Gallbladder Gastrointestinal stromal tumor	Present as thick-walled GB which on Immuno Histo chemistry (IHC) shows CD117 and c KIT positivity, has both malignant and benign counterparts[13]	Simple cholecystectomy for benign and radical cholecystectomy for malignant variant is advised however, definitive guidelines are lacking as the disease is rare.
Vascular malformations in the Gall bladder	thick-walled GB with presence of spontaneous hemorrhage and hemobilia[14]	Simple cholecystectomy

Other mesenchymal tumors like lipoma, liposarcoma, rhabdomyosarcoma etc	Large tumors replacing the GB and infiltration of the adjacent structures.	Usually palliative as these tumors present at an advanced stage.

Diagnostic Investigations:

Patients with history of right upper quadrant pain are usually investigated with an initial ultrasound abdomen. The ultrasound is widely available and cheap investigation[15]. The gall stones are radiolucent and ultrasound has proved to be a reliable investigation to look at the lumen, wall thickness and status of the adjacent liver parenchyma. There are multiple signs on ultrasonogram [16] which have proved to be soft pointers towards the gall bladder cancer.

These pointers may be:

- Presence of irregular thick-walled gallbladder
- Presence of liver metastasis
- Presence of portal and periportal lymphnodes
- Presence of ascites and peritoneal and ommental nodules
- Infiltration of the GB mass into the adjacent liver parenchyma

Any marker towards malignant process must be further investigated with a contrast enhanced computerized tomogram (CECT) abdomen with chest (Fig 2). CECT abdomen will help the treating physician to stage the disease and assess the resectability of the tumor. The GBC which is localized to the GB and adjacent segment 4B/5 of the liver is considered resectable. Any non contaguous metastasis will be considered a stage IV disease and palliation is the only treatment adviced in this case.

Further investigations like tumor markers CA 19.9, CA 242 have been investigated for establishing the diagnosis[17].

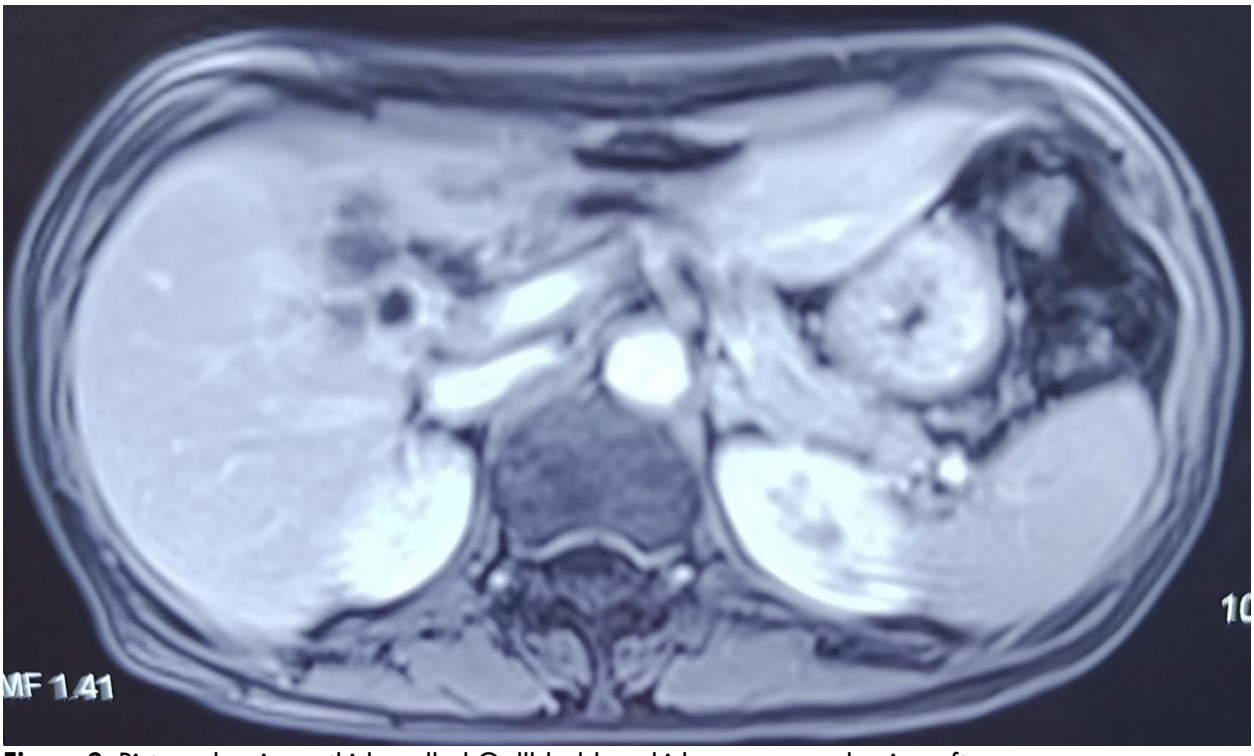

Figure 2: Picture showing a thick-walled Gallbladder which was proven benign after surgery

Tissue biopsy with fine needle aspiration cytology or a trucut biopsy is not recommended as this leads to tumor seeding. Preoperative tissue diagnosis may increase the stage of the tumor and worsen the prognosis of the affected patient.

The role of positron emission tomogram (PET) scan has been used in the staging of GBC with varying results[18]. The PET scan is relevant in cases where the diagnosis is known. However, in cases where the tissue diagnosis is unknown PET is a less relevant investigation especially in areas of TB endemicity. As the population of these areas is universally infected with TB there is always an uptake of 18 F deoxy glucose in these patients

and its sensitivity of PET scan is low in TB endemic areas [19].

The sequence of investigations mentioned in the above paragraphs(Fig 3) is the normal protocol followed for the gallbladder pathology. However, the clinical practice in this regard is confusing as lot of patients with benign diseases may present with the signs of GBC. GBC being a disease with poor prognosis, all the patients with subtle signs of malignancy on investigations are treated on the lines of malignant process until proven otherwise. However, managing these patients on the lines of malignancy may prove grevious in patients where the primary pathology is benign in nature. Subjecting these patients to morbid surgery might invite litigation in due course of treatment.

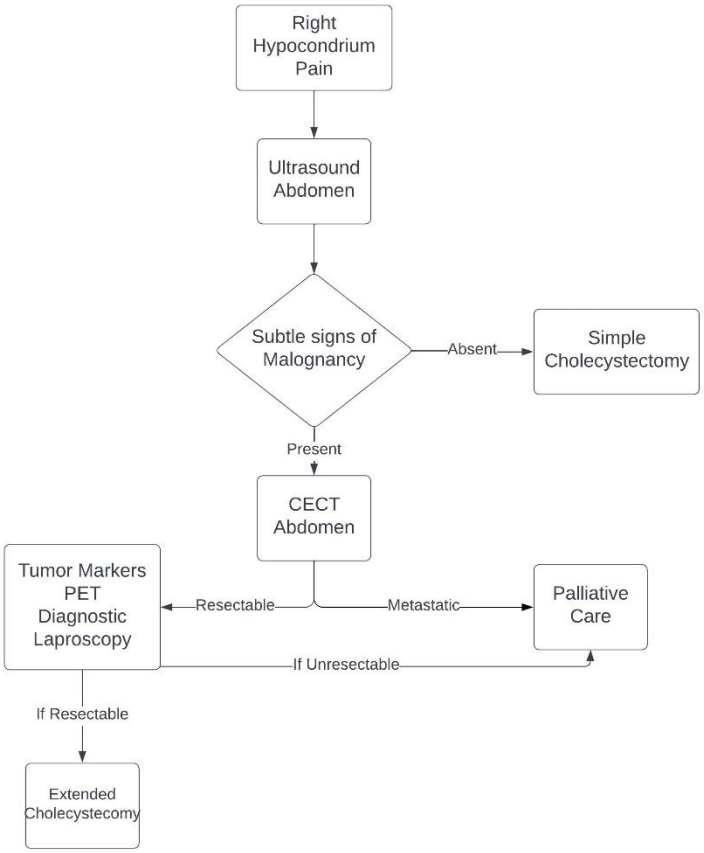

Figure 3: Flow chart of management in thick-walled Gallbladder

Differentiation of Benign and malignant masses:

The major challenges in the treatment of the patients with suspected GB malignancy is to differentiate the benign and malignant masses.

Presence of liver metastasis with ommental nodules, pulmonary metastasis or the krukenberg tumor favours the malignant process. Ommental caking, presence of generalized lymphadenopathy with GI involvement favours TB. The overlap of the signs is further complicated by the fact that certain hepatic plate dysgenesis like von meyenburg complexes [20] may be seen in patients of benign diseases producing a mirage of malignant pathology.

Furthermore, there have been reports of multiple peritoneal nodules seen on diagnostic laparoscopy which regressed after antitubercular treatment[21]. Various tumor markers have traditionally been used for this differentiation with varied results. There are newer techniques which are being proposed which can assist in preoperative planning of the management of these patients[22]. Differences have been identified in the C^{13} shift in the stones retrieved from chronic cholecystitis and cancer. These were done using nuclear magnetic resonance imaging on the stones retrieved from the cholecystectomy specimen[23]. Several chemical markers expressed

in the bile of the malignancy can assist in the preoperative determination of the nature of the disease. Koopmann et al[24] in their study demonstrated the effective use of biliary aspirates by measuring Mac 2 binding protein in conjunction with Ca 19.9 in patients of biliary tract cancer. S100A10 and Haptoglobin has been differentially expressed in tissues of GBC when it is determined using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS)[25].

Tumor related messenger ribonucleic acids (m-RNA) can be assessed in patients with malignancies. Cytological examination along with the expression of hTERT mRNA in bile from the suspected cases of GBC has increased the diagnostic accuracy[26]. Further studies on micro RNA expression in the patients can be used as potential biomarker in GBC[27]. Certain lowmolecular weight metabolites pteridines, circulating tumor cells,cell free nucleic acids, copies of mitochondrial DNA, plasma membrane proteins and autoantibody signatures are in stage of trial and can emerge as potential markers of malignancy in times to come[28-31].

Treatment strategy for thick-walled GB:

All thick-walled GB must be considered as malignant until proven otherwise. The treatment strategy involves staging work up followed by diagnostic laparoscopy. The gall bladder along with the liver wedge (Fig 4) is excised and subjected to frozen section. The tissue if negative for cancer warrants no surgery however, if the malignant cells are present completion extended cholecystectomy offers the best chance of survival in these patients.(Fig 5)

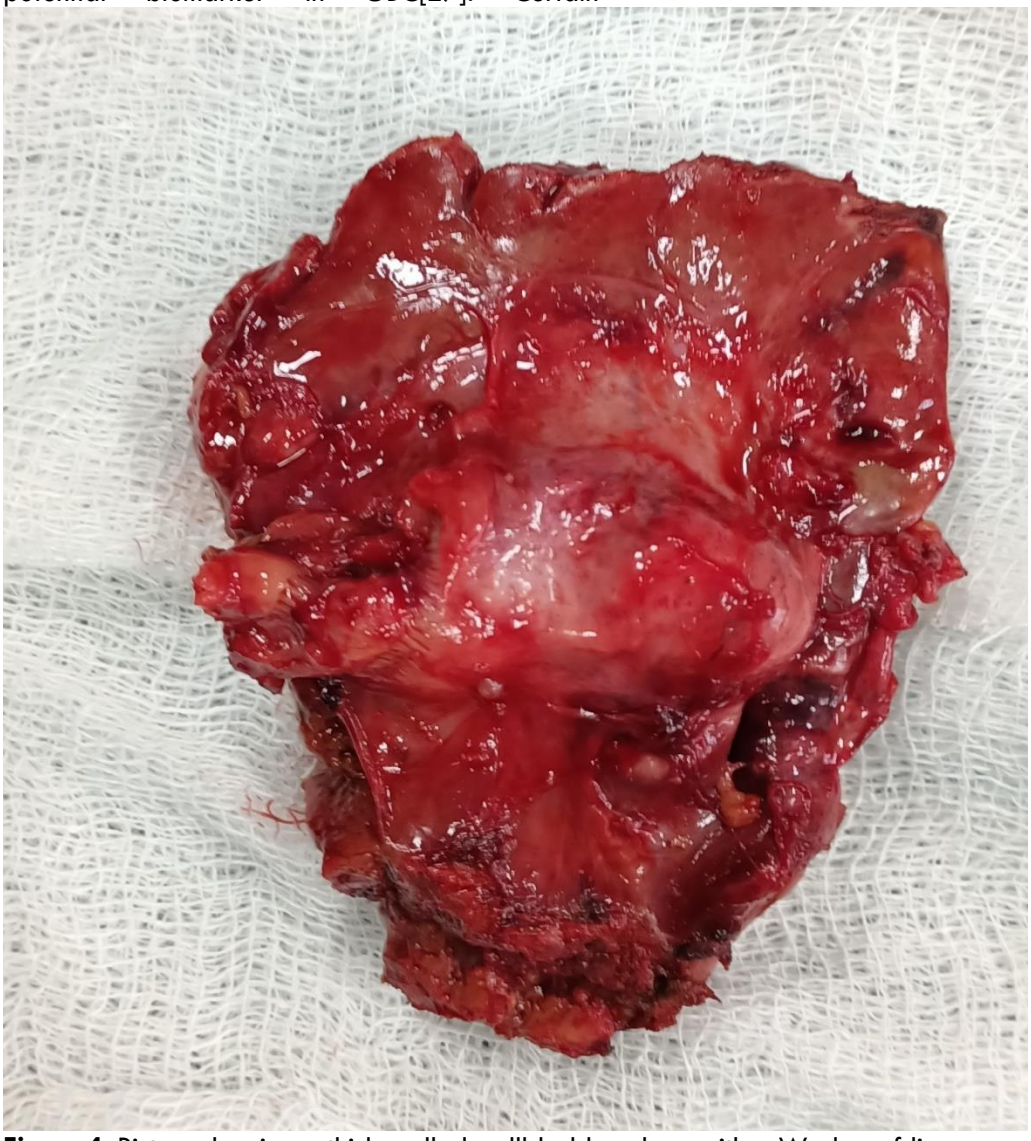

Figure 4: Picture showing a thick-walled gallbladder along with a Wedge of liver

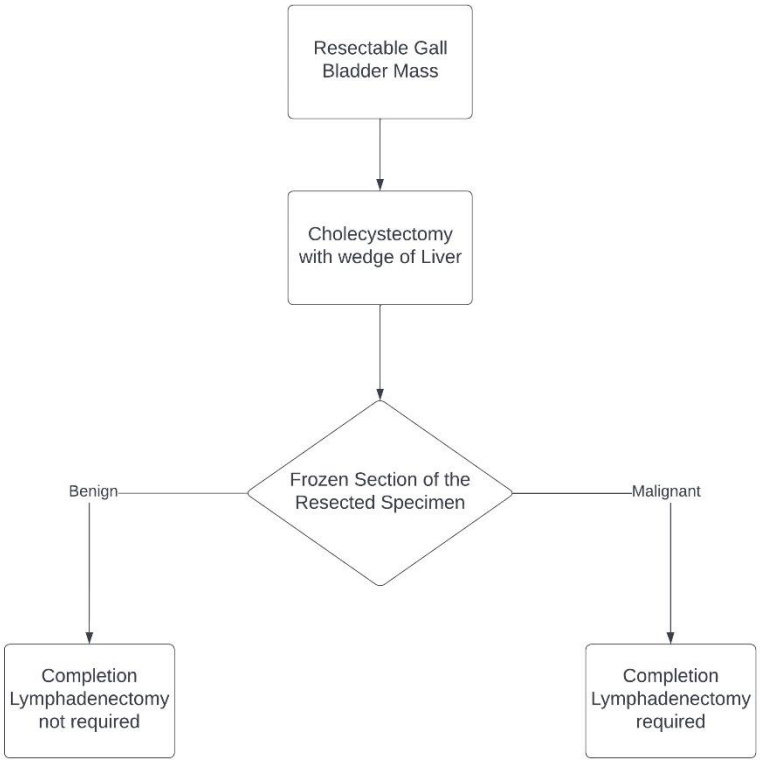

Figure 5: Flow chart to show the surgical approach to a thick-walled Gallbladder

Disscussion:

The gallbladder pathologies are commonly encountered in the indo gangetic belt of India, Pakistan and Bangladesh. Presence of poverty and malnutrition in these areas leads to the endemicity of the TB infection [32]. Several etiologies have been proposed for the endemicity of GBC in this belt. However, the definitive agents have not been established in various studies. Coexistence of cancer and malignancy in the gallbladder has been rarely known, however there are multiple case reports where the TB infection of the gallbladder was mistakenly treated as a malignancy[33].

Various diagnostic approaches have been used to stage the cancer. However, the differentiation between the malignancy and benign pathologies is challenging as tissue diagnosis is not available in majority of the cases. Preoperative fine needle aspiration or the trucut is only indicated in the locally advanced or metastatic cases where role of upfront surgery is questionable.

Extended cholecystectomy is a morbid procedure where the morbidity rates varies between15-35% depending upon the extent of the liver resection, bile duct resection or the resection of the associated involved viscera. The strategy explained above appears to be safe and cause less morbidity for a benign pathology.

Conclusion:

GBC is a dreadful disease with poor survival rates.

All thick-walled GB must be considered as malignant until proven otherwise

The presence of TB in the endemic zone of GBC further complicates the treatment strategy.

The resected cholecystectomy specimen must be subjected to histopathological examination especially in the areas of endemicity of GBC.

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