

ORIGINAL ARTICLE

*Histopathological Spectrum of Lesions of Gall Bladder*Amruta S. Jujgar¹, Alka V. Gosavi², Pallavi U. Waghmare³, Yasmin. A. Momin⁴ and Neha R. Gudale⁵

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Abstract:

Background: Gall bladder diseases exhibit a wide spectrum ranging from non-neoplastic diseases to the neoplastic. Cholecystectomy is a commonly performed abdominal surgery. Clinical diagnosis of gall bladder lesion is done based on history, physical examination and radiological findings. However, histopathological study is the gold standard method. **Material and Methods:** This was an observational study conducted in the Department of Pathology. Total number of specimens included was 204, maximum being cholecystectomy specimens. After proper gross examination with routine tissue processing; detailed microscopic examination was done. **Results:** Age of the patients ranged from 2-95 year with a mean age of 48.04 year. There was a female preponderance. Non-neoplastic lesions were more common than neoplastic. Chronic cholecystitis with cholelithiasis was the most common histopathological diagnosis. **Conclusion:** Histopathological examination of the gall bladder many times reveals an unusual diagnosis which may be missed radiologically and clinically thereby proving it to be the gold standard method.

Keywords: Cholecystitis, Cholelithiasis, Adenocarcinoma of gall bladder.

Introduction:

The gall bladder is a surgically important organ of the body and may get affected by a variety of pathological processes, which are often, under evaluated. Biliary disorders affect considerable proportion of the population. Lifestyle factors like indulgence in unhealthy fat-rich food, lack of exercise, obesity, sedentary lifestyle have increased the incidence of gall stones and diseases of the gall bladder.^[1] Gall bladder lesions present as pain in epigastrium and right upper quadrant of abdomen, usually associated with nausea, vomiting, jaundice, anorexia, fever and chills.^[2] Gall

bladder shows a wide spectrum of diseases ranging from nonneoplastic diseases like congenital anomalies, calculi to the neoplastic lesions.^[3] Cholecystitis and cholelithiasis appear to be increasing in incidence in India and western world due to increased intake of fatty and high calorie diet and use of alcohols.^[4] Cholecystitis and cholelithiasis are very common particularly in fatty, fertile, female of forty to fifty years but equally affects male and children.^[5] Cholecystitis can be broadly divided into acute or chronic cholecystitis which may be calculus or acalculus. Variants of chronic cholecystitis include eosinophilic cholecystitis, follicular cholecystitis, xanthogranulomatous cholecystitis. Benign neoplasms affecting the gall bladder include adenomas and intracystic papillary neoplasm. Malignant neoplasms of gall bladder include most commonly adenocarcinoma and rarely occurring adenosquamous carcinomas, squamous cell carcinoma, small cell carcinoma, lymphomas and sarcomas.^[6] As gall bladder itself is a non-vital organ, the treatment of choice for all gallbladder lesions irrespective of their nature or underlying disease process, is cholecystectomy.^[7] After cholecystectomy, the current practice is to send all the cholecystectomy specimens for routine histopathological examination. The rationale behind this approach is that incidental gallbladder carcinoma is found in about 0.5-1.1% of these patients, which is not detected on preoperative workup or intra-operatively. Also, early-stage gallbladder carcinoma may be difficult to distinguish from chronic cholecystitis, as they both present as a thickened gallbladder.^[8] Definitive diagnosis of gall bladder lesions is possible only after histopathologic examination, as pre-operative imaging techniques may fail to identify these lesions.^[1] Hence, the present study was undertaken to analyze the histopathology of various gall bladder lesions correlating with the available clinical parameters.

Material and Methods:

This was an observational study carried out in the Department of Pathology, at a tertiary care hospital for a

period of 1 year and 6 months. The data collected was retrospective as well as prospective. The retrospective data was collected from the requisition forms and histopathology reports of the patients. All the slides were reviewed and then included in the present study. The prospective study included all the gallbladder specimens received in the histopathology section. Resected gallbladder specimens were sent in 10% formalin either intact or as already opened up specimens or biopsies from the gall bladder. The unfixed specimens were fixed again in 10% formalin. All specimens were examined grossly for the presence of stones, growth, polyps, ulceration and other gross abnormalities. The size of the gall bladder, shape, external surface, wall thickness and the nature of mucosa were noted. After gross examination, representative tissue was subjected for routine tissue processing. Tissue sections were stained with Hematoxylin and Eosin. Detailed microscopic study was done under light microscope and then final diagnosis was given.

Results:

This study consisted of an analysis of 204 gall bladder excision or biopsy specimens received in the histopathology section of the Department of Pathology. During the study period, gall bladder specimens constituted 1.72% of total surgical pathology specimens. The age of the patients ranged from 2-95 year. The mean age of presentation was 48.04 year. The youngest patient was a 2-year-old girl child while the oldest case was a 95-year-old man. Majority of the cases were seen in the 4th, 5th and 7th decade of life. There was a female preponderance with male: female ratio being 1:1.76. Clinical presentation of patients was varied. Most of the patients presented with pain in right hypochondriac region which was associated with vomiting or fever or nausea or lump in some patients. Among 204 gall bladder specimens received, 202 were cholecystectomy specimens while only 2 were received as biopsy. Cholecystectomy specimens were examined in view of its size, shape, wall thickness, serosal and mucosal aspects. Majority of the specimens were normal in size and shape. The wall was thickened in 18.8% of the cases. The serosa was normal in majority of the cases. In some cases, serosa was congested or/and covered by exudate and in few cases, perforation was found. Majority of the specimens showed normal velvety mucosa. Gall bladder lesions were broadly classified as non- neoplastic and neoplastic lesions. Thus, Cholecystitis was the most commonly observed lesion constituting the bulk of cases (93.63%). Among 191 cases of cholecystitis, 139 cases were associated

with cholelithiasis (72.77%). Cholelithiasis was seen most commonly associated with cholecystitis (72.77%).

Table 1. Lesions of gall bladder

	No. of cases	Percentage
Non neoplastic lesions	201	98.53%
Neoplastic lesions	3	1.47%
Total	204	100%

In our study, non-neoplastic lesions of gallbladder were more common than neoplastic lesions.

Table 2. Distribution of various gall bladder lesions and its association with cholelithiasis

Diseases	Total No. of cases	Percentage of cases	No. of cases associated with Cholelithiasis
Cholecystitis	191	93.63%	139
Cholesterosis	8	3.92%	7
Adenomyoma	2	0.98%	2
Malignancy	3	1.47%	-
Total number of cases	204	100%	148

Table 3. Distribution of various cases of cholecystitis and associated with cholelithiasis

Cholecystitis	Calculus	A calculus	Total No. of cases	Percentage
Acute cholecystitis	2	11	13	6.81%
Acute gangrenous cholecystitis	1	2	3	1.57%
Acute on chronic cholecystitis	17	6	23	12.04%
Chronic cholecystitis	105	31	136	71.20%
Other variants	14	2	16	8.38%
Total	139	52	191	100%

Chronic cholecystitis was the most common type of cholecystitis found. Out of 136 cases of chronic cholecystitis, 105 cases were associated with cholelithiasis (77.21%). Thus, chronic cholecystitis with cholelithiasis was the most common lesion found in our study. **Acute Cholecystitis:** This condition was more common in young age group with male predominance. Grossly, the gall bladder was swollen, inflamed with exudate (Fig 1A). Microscopic examination revealed

mucosal ulceration with dense infiltration by neutrophils (Fig 1B). There was evidence of perforation (fig 2) in six cases. **Acute gangrenous cholecystitis:** Grossly, the specimens showed blackish discolouration. Microscopically, the epithelium was non-viable. The wall showed transmural necrosis with infiltration by polymorphs and mononuclear cells. (Fig3). **Chronic cholecystitis:** There were 136 cases. It was more common in 4th and 5th decade with female preponderance. The mean age was 47 years (Fig 4). Among other variants, follicular cholecystitis (Fig 5) was the most common cholecystitis. **Cholelithiasis:** Out of 204 cases, 148 cases had gall stones; 52 cases had single gall stone while 96 cases had multiple stones.

Table 4. Distribution of types of gall stones

Type of gall stone	Number	Percentage
Pigment	122	82.43%
Cholesterol	19	12.84%
Mixed	7	4.73%
Total	148	100%

Pigment stones were the most common and identified as multiple, small, jet black or brown coloured stones followed by cholesterol stones which were identified as solitary, oval, yellowish white in colour. Mixed stones were multiple, multifaceted and of variable size (Fig 7). Gall stones were more commonly seen in 4th and 5th decade. Out of total 130 female patients, 102 patients had gall stones (78.46%) while among total 74 male patients, 46 patients showed evidence of gall stones (62.16%) giving M: F ratio of 1:1.37. **Cholesterolosis:** There were 8 cases of cholesterolosis. All the cases showed focal cholesterolosis and all were associated with chronic cholecystitis. On microscopy, it showed infiltration by lipid laden foamy macrophages into the lamina propria (Fig 6). Age of patients ranges from 34-55 years. Out of 8 cases, 1 was male and 7 were females with male : female ratio being 1:7. **Adenomyoma:** There were 2 cases of adenomyoma, a 25-year-old lady and a 48-year-old man. Grossly, the specimens showed focal thickening of wall at the fundus. Both the cases were associated with cholelithiasis. Microscopically, the wall showed a circumscribed lesion with many Rokitansky- Aschoff sinuses surrounded by hypertrophied smooth muscles. **Epithelial changes:** The various types of epithelial alterations include epithelial hyperplasia, spongoid hyperplasia, atrophic mucosa, atrophic epithelium with focal hyperplasia, mucosal ulceration non-viable epithelium and antral metaplasia (Fig 8). Among these, antral metaplasia was the most common epithelial alteration followed by

epithelial ulceration. Antral metaplasia was associated with various types of cholecystitis, and was most commonly associated with chronic cholecystitis. Lushka ducts, Rokitansky- Aschoff sinuses were also most commonly associated with chronic cholecystitis. **Neoplastic lesions:** In the present study, only three neoplasms of gall bladder were seen. All were malignant. There were 2 cases of adenocarcinoma and a single case of Non-Hodgkin Lymphoma. The first case was a 60-year-old lady, presented with pain in abdomen for 8 days. Clinical diagnosis was perforation of gall bladder. The cholecystectomy specimen was received in pieces and revealed thickened gall bladder covered with exudate. Malignancy was not suspected radiologically, clinically as well as on gross examination. But microscopy revealed well differentiated adenocarcinoma infiltrating the wall of gall bladder with perforation peritonitis. (Fig 9) The second case was a 36-year-old man, presented with pain in abdomen. No abdominal lump was found on clinical examination. CT scan showed a nodular mass at the fundus of gall bladder, biopsy from the mass was performed which revealed poorly differentiated adenocarcinoma. The third case was a 41-year-old lady who was HIV positive.

Table 5. Histopathological spectrum of gall bladder lesions

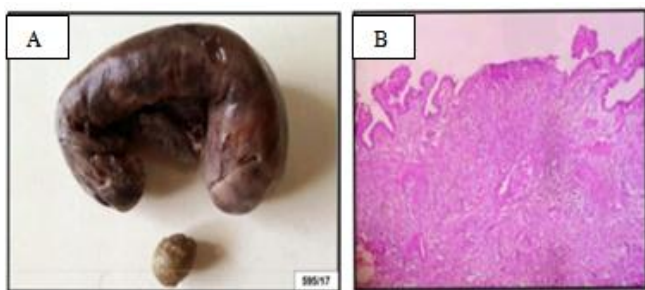
Sr. No.	Lesion	No. of cases	Percentage
1	Acute cholecystitis	16	7.84%
2	Acute on chronic cholecystitis including choledochal cyst and perforation peritonitis	23	11.27%
3	Chronic cholecystitis including choledochal cyst and perforation peritonitis	136	66.68%
4	Eosinophilic cholecystitis	2	0.98%
5	Follicular cholecystitis	8	3.92%
6	Xanthogranulomatous cholecystitis	6	2.94%
7	Cholesterolosis	8	3.92%
8	Adenomyoma	2	1.35%
9	Adenocarcinoma	2	0.98%
10	Non-Hodgkin Lymphoma	1	0.49%

Abdominal ultrasonography revealed a mass in the gall bladder. The histopathological examination of the mass

revealed the diagnosis of Non-Hodgkin Lymphoma and immunohistochemistry was advised for confirmation.(Fig 10) In our study, a wide spectrum of lesions of gall bladder were observed. The histopathological spectrum of gall bladder in the present study includes non- neoplastic lesions like calculus or acalculus acute cholecystitis, chronic cholecystitis, cholecystitis with choledochal cyst, cholecystitis with perforation peritonitis, follicular cholecystitis to neoplastic lesions like carcinoma and lymphoma.

Figure 1A- Gross specimen of acute cholecystitis showing enlarged, inflamed, edematous gall bladder with marked serous congestion along with gall stone

Fig 1B -Microscopic image of acute cholecystitis



showing mucosal ulceration(H&E X100)

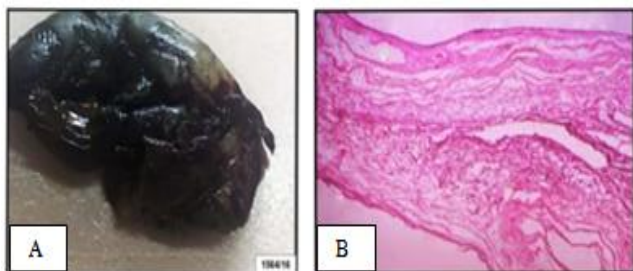
Figure 2: Gross specimen of gall bladder showing perforation. The serosa shows marked congestion



and is covered by exudate.

Figure 3A- Gross specimen of acute gangrenous cholecystitis showing blackish discolouration of gall bladder

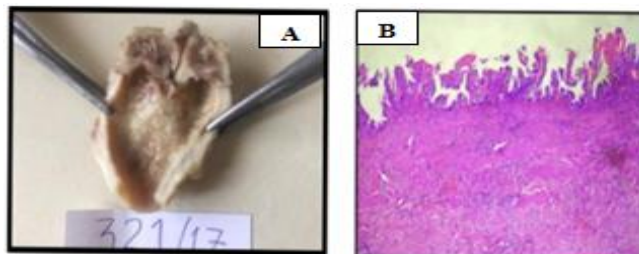
Figure 3B -Microscopic image of acute gangrenous cholecystitis showing necrosis of gall bladder wall.



(H&E X100)

Figure 4A- Gross specimen of chronic cholecystitis showing thickened wall of gall bladder

Figure 4B -Microscopic image of chronic cholecystitis showing thickened wall of gall bladder with marked fibrosis and diffuse and dense



infiltration by mononuclear cells (H&E X100)

Figure 5: Microscopic image of follicular cholecystitis showing 5A - Lymphoid follicles in lamina propria

and in the wall of gall bladder (H&EX100) 5B- lymphoid follicles throughout the wall of gall bladder(H&EX100)

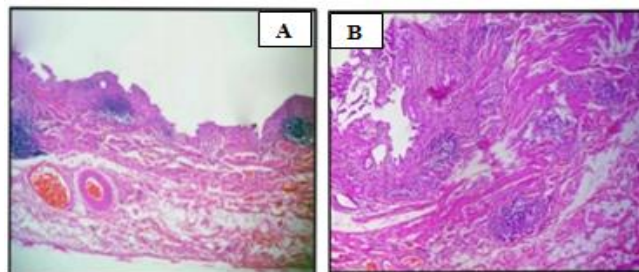


Figure 6 : Photomicrograph of Xanthogranulomatous cholecystitis showing sheets of Xanthoma cells (arrow) admixed with histiocytes and mononuclear cells (H&E, X100)Inset showing xanthoma cells (H&E, X400)

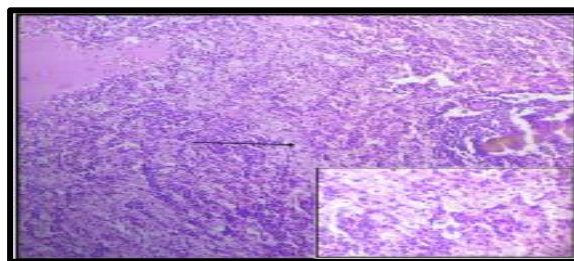


Figure 7: Gross specimen of gall bladder showing A) Multiple pigment stones B) Cholesterol stones C) Multiple mixed stones

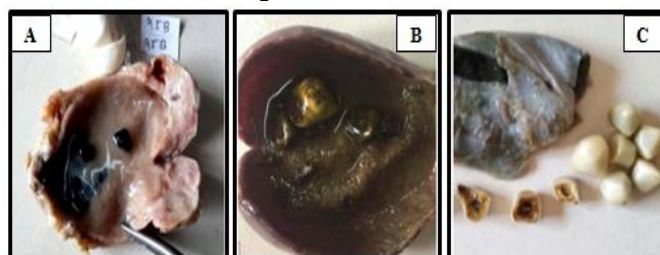


Figure 8 : Photograph of gall bladder showing antral metaplasia(H&Ex100)

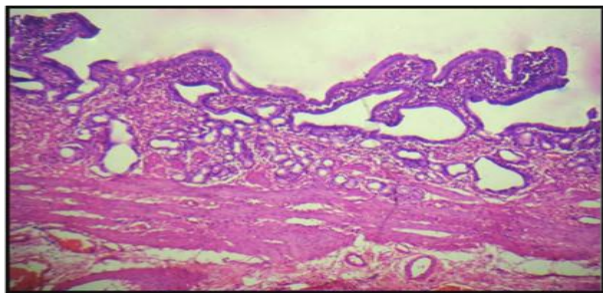


Figure 9 : Microscopic image of well differentiated adenocarcinoma of gall bladder (H&E X100). Inset showing glands with cytological atypia (H&E, X400)

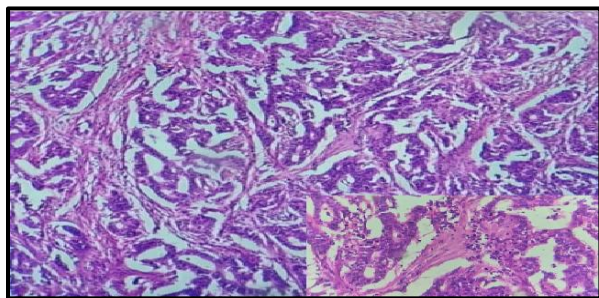
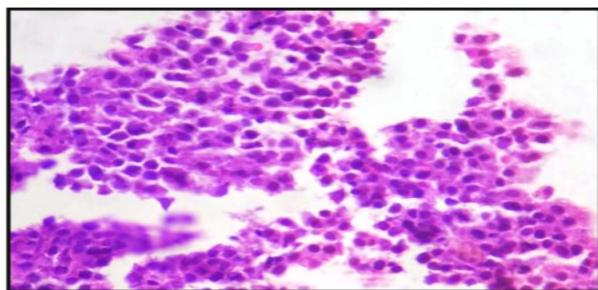


Figure 10: Photomicrograph of Non-Hodgkin Lymphoma of gall bladder (H&E X400)



Discussion:

Gall bladder diseases are prevalent worldwide affecting a significant portion of population and present with a diverse clinical and histopathological spectrum.^[9] Histopathological examination many times reveal an unusual diagnosis bearing significant implications on the treatment, prognosis and outcome of the patient. In the present study, gall bladder specimens constituted a minor component (1.72%) of total surgical pathology specimens which is comparable with study done by Rashmi H K et al.^[10] Findings of age and sex distribution in this study are in concordance with the studies done by Damor NT et al,^[3] Sharma I et al^[6] and Anushree CN et al^[11] Gall bladder diseases are seen predominantly affecting females as compared to males.

Possible, female sex hormones appear to play a significant role in the formation of gall stones, especially between the ages of 20 and 30 years.^[12] Human gall bladder has oestrogen and progesterone receptors thus making female sex hormones as predisposing factors for cholelithiasis.^[13] According to Selvi RT et al, oestrogen stimulates the HMG-Co-A reductase enzyme causing increased synthesis of cholesterol and thus putting women at an increased risk of supersaturation.^[12] Although clinically most of the gall bladder lesions present as pain in right hypochondriac region, morphologically the lesion may vary from infective to neoplastic etiology.^[1] As seen in our study, most of the cases of calculus and acalculus cholecystitis as well as all three cases of malignancy presented with pain in abdomen. Damor NT et al^[3] and Shah H et al^[2] found that the non-neoplastic lesions of gall bladder were common than the neoplastic ones which is concordant with our study. Chronic cholecystitis was the commonest histopathologic finding in present study, similar finding is observed by Kumari NS et al^[1], Kumbhakar D et al^[14] and Shah H et al.^[2] Acute gangrenous cholecystitis is the last stage of gall bladder inflammation resulting from progressive vascular compromise and ischemia causing necrosis of the gall bladder wall and may lead to perforation. Various factors like diabetes mellitus, advanced age, increased C reactive protein level and associated cardiovascular disease increase the probability of acute gangrenous cholecystitis.^[2] Gall stone disease is a fairly common condition at global level and constitutes more than 90% of biliary tract disease.^[11] It is commonly found in fatty, fertile, female of forty to fifty years, but it can also be seen in men and children.^[15] Cholesterol and mixed stones are formed from biliary sludge while pigment stones are composed of calcium salts of unconjugated bilirubin with varying amounts of cholesterol and protein.^[16] Pigment stones form as a result of increased unconjugated bilirubin in the bile, which then forms insoluble calcium salts. Eosinophilic cholecystitis (EC) is a rare and poorly understood disease of the gallbladder.^[17] As there is no specific clinical presentation of eosinophilic cholecystitis, histopathological evaluation is the main modality for diagnosing this condition.^[18] Eosinophilic cholecystitis (EC) is said to be present when the transmural eosinophils infiltration is more than 90%. Peripheral eosinophilia may or may not be present. It has been hypothesized that EC may be caused by hypersensitivity to bile acids. Cases have also been reported secondary to infections, parasitosis, allergies, hyper-eosinophilic syndrome, eosinophilic gastroenteritis, drugs and herbal medicines.^[17] The treatment of choice remains cholecystectomy.^[18] Carcinoma of the gall bladder

though generally considered rare, is the most common malignancy of the biliary tract, accounting for 80-95% of biliary tract cancers.^[19] Gall bladder carcinoma is the malignancy with poor prognosis and high fatality.^[20] Kumbhakar D et al^[14], Kathuria V et al^[15] and Damor NT et al^[3] found incidence of malignant lesions of gall bladder as 1.25%, 1.09% and 2% respectively. We found 1.47% cases of malignancies of gall bladder which is comparable to the above-mentioned studies. There were three cases of malignancy in the present study, all presented with complaint of pain in abdomen. In the first case malignancy was not suspected clinically as well as radiologically. Gross examination showed thickened wall of gall bladder. The microscopy revealed well differentiated adenocarcinoma. While in other two cases radiology showed mass in gall bladder so biopsy was performed. Diagnosis of poorly differentiated adenocarcinoma and Non-Hodgkin Lymphoma were given depending on histomorphology. Immunohistochemistry was advised for confirmation, but patient lost to follow up. The origin of gall bladder lymphoma is controversial as lymphoid tissue present in the gall bladder mucosa is sparse. Some intraepithelial lymphocytes are present among surface columnar cells. Gall bladder malignant lymphoma constitutes only 0.1-0.2% of all gall bladder tumors.^[21] Secondary involvement of the gall bladder along with adjacent lymph nodes is more common than primary lymphomas of the gall bladder. Malignant lymphoma and leukemia can involve the gall bladder as a part of systemic disease; rarely this may be the initial presentation.^[22] In 2007, Ödemis et al^[23] retrospective study reported that 7 of the 1123 patients with malignant cholangiocarcinoma

were diagnosed with biliary Non-Hodgkin's lymph tumors (0.6%), and primary biliary non-Hodgkin's lymphoma accounted for 0.4% of extranodal NHL, accounting for only about 0.016% of all NHL cases. Immunocompromised patients are at increased risk of development of Non-Hodgkin lymphoma like in our case. Thus, definitive diagnosis of the malignant lesions is only possible on histopathological examination, as pre-operative imaging techniques may fail to identify the lesions. Despite all the advancement in the imaging techniques, the confirmation of malignancy can only be done by histological assessment.^[11] Malignancies of gall bladder are discovered or confirmed only on histopathological examination which is regarded as the gold standard.^[10] Thus, it is important to study the histopathological changes to know the distribution of various gall bladder lesions and for proper diagnosis and treatment.

Conclusion:

The present study revealed a wide spectrum of histopathological lesions of gall bladder. Non-neoplastic lesions of the gall bladder outnumbered the neoplastic lesions. Chronic cholecystitis with cholelithiasis was the most common histopathological diagnosis. Routine cholecystectomy done for gall stone disease gives varied histomorphological spectrum and unexpected diagnosis of malignancy, which may be missed clinically and radiologically.

Sources of Supports: Nil

Conflicts of Interest: Nil

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