Gall Bladder Malignancy: An Unusual Association

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INTRODUCTION

The carcinoma of the gall bladder is a poor prognosis malignancy that often clinically mimics benign gall bladder diseases and escapes detection until advanced stage. Primary lymphoma of the gall bladder, however, is exceedingly rare [1, 4]. We present a rare case of simultaneous development of adenocarcinoma and primary B cell lymphoma of mucosa associated lymphoid tissue (MALT) of the gall bladder.

CASE REPORT

An 83 year old British woman presented with bloating, abdominal pain and dyspepsia. The ultrasonography revealed distended gallbladder with a hypoechoic mass. She then had a computed tomography which showed a 15mm polypoidal lesion in the midpole of the gall bladder with no extension through the wall. There was no lymphadenopathy or metastatic focus.

ABSTRACT

Gall bladder malignancy predominantly comprises adenocarcinoma and is found mostly in a late stage whereas primary lymphoma of mucosa associated lymphoid tissue (MALT) within the gall bladder is exceedingly rare and has an incidental presentation. We report a case of well differentiated adenocarcinoma with MALT lymphoma of the gall bladder in an 83 year old woman. To our knowledge, this is the first case of a carcinoma and lymphoma occurring simultaneously in the gall bladder.

Key words: gallbladder – adenocarcinoma – lymphoma.

A laparoscopic cholecystectomy was performed. The gall bladder measured 75x40mm and showed an unremarkable serosal surface. On opening the gall bladder, a polypoidal mass 11x10x8mm was present in the fundus. In addition, the adjoining gall bladder mucosa showed marked diffuse nodularity but no gallstones were found in the lumen.

Histological examination from the polypoidal lesion showed a well differentiated adenocarcinoma and primary B cell lymphoma of mucosa associated lymphoid tissue (MALT) of the gall bladder.

Fig.1. Photomicrograph of the gall bladder showing well differentiated adenocarcinoma arising on a background of tubular adenoma with high grade dysplasia (H&E, 20x). Inset: Higher magnification showing foci of invasion (H&E, 100x).
The adjacent gall bladder showed multiple small firm coalescing polypoidal lesions that showed atypical lymphoid infiltrate extending from mucosa into the submucosa and focally into the muscularis propria and surrounding subserosal adipose tissue (Fig. 2A). The infiltrate appeared vaguely circumferential and consisted of scattered germinal centres surrounded by dense infiltrate of predominately small to medium sized cleaved centrocyte like cells with pale to clear cytoplasm, admixed with a few large blasts (Fig. 2B). Definite lymphoepithelial lesions were not identified. There was no involvement of the surface epithelium by this atypical lymphoid infiltrate. The lymphoid cells were positive for CD20 (Fig. 2C), BCL-2, and IgM and weakly for CD5 and were negative for CD21, CD23, cyclin D1 and IgG. Kappa and lambda light chain immunostaining was equivocal. The proliferation index by MIB-1 immunostaining was <5% (Fig. 2D). CD21 and CD23 highlighted the residual follicular dendritic cell meshwork within the germinal centres.

On PCR analysis, faint clonal rearrangements were detected at the immunoglobulin heavy chain gene locus and oligoclonal bands were noted at the light chain (kappa and lambda) gene loci. Based on the morphology, immunophenotype and the gene rearrangement analysis, a diagnosis of gall bladder involvement by low grade extra nodal marginal zone B cell lymphoma was made. The cystic duct lymph node showed reactive changes only. The carcinoma and lymphoma were limited to the gall bladder and no other lesion was detected on further examination. The patient has been maintained on regular follow up without any further treatment.

**DISCUSSION**

The carcinoma of the gall bladder is a relatively uncommon neoplasm that shows female predominance (female to male ratio, 3-4:1). It is commonly associated with gall stones (80%), porcelain gall bladder (10-20%) and abnormal choledochopancreatic duct junction, though our case did not have any of these associations [1].

On histological examination, the tumour showed typical morphology and architecture of adenocarcinoma in our case. But it can be difficult at times to distinguish well differentiated adenocarcinoma of the gall bladder from Rokintansky-Aschoff sinuses, which can be located throughout the gall bladder wall, even extending into the perimuscular adipose tissue. These potential pitfalls have been reviewed by Giang et al and they have emphasized the importance of thorough sampling, particularly in older patients and close examination of any deeply situated glandular structures and mural thickening as being critical in the diagnosis [1].

Most cases exhibiting severe chronic lymphocytic infiltration within the gall bladder were classified as chronic follicular cholecystitis and were associated with ascending infection by gram negative bacilli, prior to the establishment of MALT lymphoma as a separate disease entity [2, 3]. The association of long term gastritis caused by *Helicobacter pylori* infection and MALT lymphoma in the stomach is well known [4]. Tsuchiya et al have postulated that infection by gram negative bacilli with prolonged inflammatory status similar to that in the stomach may be an important cause of

![Fig. 2. Photomicrograph of the gall bladder. A: The adjacent gall bladder wall shows multiple small firm coalescing polypoidal lesions containing atypical lymphoid infiltrate (H&E, 20x). B: On higher magnification, the atypical lymphoid infiltrate shows scattered germinal centres surrounded by dense infiltrate of predominantly small to medium sized cleaved centrocyte like cells with pale to clear cytoplasm, admixed with a few large blasts (H&E, 100x). C: The neoplastic lymphoid cells are diffusely positive for CD20 (100x). D: The proliferation index by MIB-1 immunostaining is very low (100x).](image-url)
low grade MALT lymphoma of the gall bladder. In addition, he has put forth that repeated pancreatitis may be associated with chronic inflammation of the pancreato-biliary system [4]. Recently the theory of antigenic stimulation causing chromosomal translocation that result in the formation of a fusion protein, API2-MALT1 which inhibits apoptosis by NF-κB mediated up regulation of apoptotic inhibitor genes and induces antigen independent proliferation with formation of MALT lymphoma has been favoured [5]. Bisig et al have described a case of gall bladder MALT lymphoma with t(11; 18) (q21; q21) similar to that seen in the stomach. Further molecular and chromosomal studies need to be done to understand this rare tumour [6].

Histological diagnosis of MALT lymphomas at various sites encountered has been very challenging and rests on morphological features combined with ruling out other malignant B-cell lymphoproliferative disorders based on a battery of immunohistochemical stains [5]. The morphology of lymphoid follicles surrounded by centrocyte-like B cells infiltrating the crypt epithelium, the immunohistochemical profile and PCR analysis all support the diagnosis of MALT lymphoma in our case.

Simultaneous development of carcinoma and lymphoma has been described in stomach [7], colon [8], lung [9] and prostate [10] but not yet been reported in gall bladder.

In carcinomas with dense lymphocytic infiltrate in the vicinity, it is important to remember these cells may not always be reactive. These changes should alert the pathologist to carefully assess its morphology, immunophenotype and clonality in order to rule out a coexisting MALT lymphoma and to closely scrutinize regional lymph nodes for their involvement.

In many such synchronously observed dual tumours, though lymphoma may precede carcinoma, the prognosis appears to be closely associated with the adenocarcinoma than with the lymphoma. This phenomenon can be explained by the fact that most of the lymphomas are usually of the low grade [7].

Conflicts of interest: None to declare.

REFERENCES