Gall Bladder and Extrahepatic Bile Duct Lymphomas:
Clinicopathological observations and biological implications

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Abstract

Lymphomas of the gall bladder and extrahepatic bile ducts are exceedingly rare. We present the clinicopathological features of 19 cases from our files; 14 patients had primary lymphoma (13 involving gall bladder and one involving common hepatic duct), while five had systemic lymphoma on further work-up. Most patients presented with symptoms mimicking cholecystitis. The most common primary lymphoma types were diffuse large B-cell lymphoma (DLBCL), extranodal marginal zone lymphoma (EMZL), B-lymphoblastic lymphoma (B-LBL) and follicular lymphoma (FL). Two cases had features of lymphomatous polyposis, one a case of FL and the second a case of mantle cell lymphoma (MCL), with disease limited to the mantle zones, so-called *in situ* MCL. Other rare lymphoma subtypes not previously described in this site included the extracavitary variant of primary effusion lymphoma (PEL) and plasmablastic lymphoma (PBL). Patients with DLBCL and EMZL were older (mean age 75.8 years) than those with other subtypes (mean age 47 years) and more likely to have gallstones (60% vs. 12.5%). A comprehensive literature review revealed 36 primary gall bladder and 16 primary extrahepatic bile duct lymphomas. When compared to primary gall bladder lymphomas, those involving the extrahepatic bile ducts present at a younger age (47 years vs. 63 years) usually with obstructive jaundice, and are less often associated with gallstones (17% vs. 50%) or regional lymph node involvement (6% vs. 31%). In conclusion, primary lymphomas of the gall bladder and extrahepatic bile ducts show a broad spectrum of disease types, but in many respects mirror the spectrum of primary lymphomas of the gastrointestinal tract.

Keywords

lymphoma; gallbladder; bile duct; hepatic duct; cystic duct; cholecystitis; cholelithiasis; extranodal; intestinal follicular lymphoma; in situ mantle cell lymphoma; HHV-8/KSHV; plasmablastic lymphoma; primary effusion lymphoma; lymphomatous polyposis

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Introduction

Lymphoma of the gall bladder is exceedingly rare with only anecdotal cases reported in literature. We present the largest series of gall bladder lymphomas to date, based on a retrospective study of 19 cases in our files. Fourteen patients had only loco regional involvement (i.e. primary lymphoma), of which one had lymphoma involving the common hepatic duct without gall bladder involvement. Five patients who presented with gall bladder disease had systemic lymphoma on further work-up. In most instances the presenting symptoms mimicked cholecystitis. Histologically, there was a diverse spectrum, including many subtypes not previously documented in the gall bladder such as mantle cell lymphoma, plasmablastic lymphoma, primary effusion lymphoma, and post-transplantation lymphoproliferative disorder of T-cell type. In addition, we have also reviewed all the cases reported in literature and present the clinicopathological features of primary gall bladder and bile duct lymphomas.

Materials and methods

All cases with lymphomatous involvement of the gall bladder were retrieved from our consultation files. This study was approved by the Institutional Review Board of the National Cancer Institute (IRB protocol No. 10-C-N 074). Cases in which lymphoma was restricted to the gall bladder with or without regional spread were identified, based on available and follow-up information from referring pathologists and clinical charts. Additionally, we identified cases in which gall bladder involvement was the initial clinical manifestation of disease, even when subsequent evaluation revealed that the disease was not restricted to the gall bladder. However, cases with a known prior diagnosis of lymphoma were excluded from study.

Clinical details, gross descriptions, and histological slides were reviewed. All cases were classified according to the World Health Organization (WHO) classification (2008) for hematolymphoid neoplasms(61). Immunostains performed on all cases included CD20, CD3, Kappa and Lambda. Additional pertinent studies were performed in selected cases based on the histologic differential diagnosis and included immunohistochemistry (CD79a, PAX5, CD2, CD5, CD4, CD8, CD43, CYCLIN D1, CD10, BCL2, BCL6, Ki 67, IgD, IgG, IgA, IgM, CD30, CD15, MUM1, CD138, P53, TdT, CD99, HHV8), in situ hybridization for EBV (EBER), and molecular studies [*IGH@* and *TCR* gamma gene rearrangements, fluorescence in situ hybridization (FISH) for t(14;18)(q32;q21), t(11;14)(q13;q32) and t(8;14)(q24;q32)). *IGH@* and *TCR* gamma gene rearrangements were identified by PCR analysis of DNA extracted from formalin fixed paraffin embedded tissue. *IGH@* PCR was performed using consensus primers to framework region (II and/or III) and the joining region of the immunoglobulin heavy chain gene(54), while *TCR* gamma gene PCR was performed using two separate primer sets with primers Vg101, Vg11 and Jg12 (set 1) and primers Vg 101, Vg11 and Jp12 (set 2)(42).

A literature search was performed in PubMed using search words including gall bladder, bile duct, cystic duct, and lymphoma, lymphoproliferative disorder or atypical lymphoid hyperplasia. Publications were retrieved and reviewed to identify cases of primary gall bladder/bile duct lymphoma. A few additional cases that had not been retrieved in the PubMed search were identified by cross-references within the retrieved publications. All available clinical and pathology data were tabulated.

Results

Clinical and pathological features – NIH cases

We identified 14 primary lymphomas, 13 involving the gall bladder and one involving the extrahepatic bile ducts (Table 1). Patients were 5 to 84 (mean 57) years in age and included 10

males and four females. Eleven of 12 cases (92%) with gall bladder lymphoma presented with symptoms of cholecystitis, cholelithiasis or jaundice, while one case was detected incidentally; no details were available in two cases. Three patients were immunocompromised (2 HIV positive; 1 post-transplant), while two additional patients had colon cancer. Three of the 14 patients (23%) had B-symptoms. Four of 11 cases (36%) had gallstones. Regional lymphadenopathy was intraoperatively identified in six cases. Histologically, regional lymph nodes were involved by lymphoma in three of these six (50%) cases, while local contiguous spread to surrounding soft tissue was present in two additional cases without nodal involvement. There was a single case (case # 4) with a common hepatic duct mass, without gall bladder involvement. This patient had undergone a gastric bypass surgery three years prior to presenting with obstructive jaundice; there were no gall stones or regional lymphadenopathy. None of the 14 cases had systemic disease.

Three cases of diffuse large B-cell lymphoma (DLBCL) were identified (3/14; 21.5%). Following the Hans immunohistochemical algorithm(26), two of three were of germinal center B-cell type, one of them with the t(14;18) involving the *BCL2* and *IGH@* genes. Two cases of follicular lymphoma (FL), Grade 1–2, were observed, one of which presented as a localized polypoid lesion of the mucosa (case #6). A third case of FL (case #4) presented in the common bile duct and was Grade 3B. Two cases (2/14; 14.3%) of extranodal marginal zone lymphoma (EMZL) were seen (Fig. 1), both of which showed extensive mucosal involvement. One case of mantle cell lymphoma (MCL) (case # 8) had features of lymphomatous polyposis (Fig. 2). It exhibited limited involvement of the mantle zones with neoplastic cells surrounding reactive germinal centers. It was CD5-negative but SOX11+, and was positive for the t(11;14) by FISH. A colonic resection performed at the same time for colonic adenocarcinoma showed no involvement by lymphoma.Two HIV-associated lymphomas were identified: a solid variant of primary effusion lymphoma (PEL) (case # 3) (Fig. 3) and plasmablastic lymphoma (PBL) (case # 5) (Fig. 4). Two patients presented with B-lymphoblastic lymphoma (B-LBL) as the sole manifestation of disease. The single patient with T-cell lymphoma was a 5-year-old boy (case #1) who was status post-cardiac transplant on tacrolimus and presented with cholecystitis. Histologically, there was transmural involvement by a clonal T-cell infiltrate, negative for EBV by EBER-ISH.

Histologically, there was transmural involvement by lymphoma in ten cases (71.4%), while four cases (28.6%) showed relative mucosal sparing with predominant smooth muscle and adventitial involvement. The four cases with relative mucosal sparing included two patients with DLBCL (case # 9 and 13) and one patient each with plasmablastic lymphoma (case # 5) and B-LBL (case # 12).

Patients with DLBCL (cases # 9, 11, 13) and EMZL (cases # 10, 14) were older (72 to 84 years, mean 75.8 years) than those with other subtypes (5 to 74 years, mean 46.6 years). Gallstones were present in two of three cases (66%) with DLBCL, one of two cases (50%) with EMZL, and only in one of eight (12.5%) cases with other lymphoma subtypes.

An additional five patients without a prior diagnosis of lymphoma presented with symptoms of gall bladder disease and were diagnosed with lymphoma following cholecystectomy (Table 2). Unlike the first group of patients wherein the disease was restricted to the gall bladder and regional lymph nodes, these five patients had widespread disease on further work-up. Thus, although they had systemic involvement by lymphoma, they had come to clinical attention due to gall bladder involvement. These five patients ranged in age from 38 to 85 years (mean 64.8 years) and included three females and two males. Four patients (80%) had B-symptoms. One patient had Sjogren syndrome; none were immunocompromised. Only one of four patients (25%) with available gross description had gall stones. Three patients (60%) had regional lymphadenopathy at surgery, while all had systemic involvement on follow-up. Histologically,

one patient had classical Hodgkin lymphoma, while the remaining four had B-cell lymphomas. One case was a DLBCL with a double-hit translocation involving the *BCL2* and *MYC* genes. All five cases (100%) showed transmural involvement of the gall bladder wall.

Clinical and pathological features – Literature cases

The review of literature identified 52 cases of primary biliary lymphoma including 36 involving the gallbladder and 16 involving only the extrahepatic bile ducts. Most patients had presented with features suggestive of acute cholecystitis or obstructive jaundice; five were detected incidentally on imaging or surgery for unrelated conditions. The 36 patients with primary lymphoma of the gallbladder (Table 3) included 23 women and 13 men, aged 4 to 91 (mean 63) years. The most common lymphoma type was EMZL (12 cases)(1,6,7,14,[35],[43],[45],[49],53, 62,66,67), with an additional case from older literature (29) reported as "pseudolymphoma". Collectively, these 13 patients were predominantly women (11/13) with a mean age of 68 years (range 31–91 years). Of the cases with clinical information, gall stones were present in 54.5% (6/11) of cases and regional lymph nodes were involved in 20% (2/10) of cases. Of the eight cases with reported outcomes, six (75%) were alive at follow-up (from 6 months to 8 years), while two had died of unrelated diseases without recurrence of lymphoma. There were eight cases of DLBCL(13,24,28,34,51,57,70,72), with an additional case of diffuse non-Hodgkin lymphoma (NHL), not further specified(67). These nine patients averaged 64 (range 40–78) years of age without gender predilection (4 women, 5 men); 83.3% (5/6) cases had gallstones and 28.6% (2/7) cases had lymph node involvement. Only one of nine (11%) patients had no evidence of disease at 38 months(34), whereas others developed systemic disease, with three patients dying within three years of diagnosis. The four cases of follicular lymphoma (22,31, 47,69) were also predominantly women with a mean age of 71 (range 63–78) years; gallstones were present in two cases and one had regional lymph node involvement. All three patients with available follow up information (from 9 months to 3 years) were alive without evidence of disease. There were anecdotal reports of other lymphoma types including lymphoblastic lymphoma, angiotropic or intravascular lymphoma, low grade B-cell lymphoma, poorly differentiated lymphocytic lymphoma, classical Hodgkin lymphoma, and reports in older literature diagnosed as lymphosarcoma and reticulum cell sarcoma.

In 16 cases identified in the literature, the lymphoma involved only the extrahepatic bile ducts without gallbladder involvement (Table 4). These patients were 25 to 68 years old (mean 47 years) without gender predilection (9 women, 7 men) and had presented with obstructive jaundice (15/16 cases, 93.8%). Only one patient (1/15, 6.7%) had regional nodal involvement and gallstones (1/5, 20%). Of 12 patients with available follow-up information (from 6 months to 4 years), four died of progressive disease (4/12, 33%), while eight were alive and in remission. Preoperatively, all 16 patients were thought to have cholangiocarcinoma. Histologically, there were seven cases (43.8%) of high grade B-cell lymphomas (three with DLBCL, three with "diffuse small or medium cell lymphoma" and one with T-cell histiocyte rich large B-cell lymphoma (TCHRBCL). Four patients (25%) had follicular lymphoma. There was one case of EMZL, two EBV-PTLD in a post liver transplant setting, one T-cell NHL not further specified and one "NHL" not further specified. Analysis of our cases combined with those reported in literature identified certain clinicopathologic differences between lymphomas of the gall bladder and extrahepatic bile ducts. Patients with bile duct lymphoma presented at a younger age (mean 47 years) than those with gall bladder lymphoma (mean age 63 years). All patients with bile duct lymphoma were symptomatic, whereas gallbladder lymphoma was an incidental finding in a proportion of cases (8/47, 17%). There was no significant gender predilection, although women were slightly more commonly affected in both groups (59% of bile duct and 54% of gallbladder lymphomas). An association with gallstones was noted more often in gallbladder lymphomas (21/42, 50%) than in bile duct lymphoma (1/6, 17%). Regional lymph node involvement was also more frequent in gallbladder lymphomas (11/35, 31.4%,

versus 1/16, 6.3%). Among histologic types, EMZL was distinctly uncommon in the bile ducts (1/17, 5.9% of cases) as compared to the gall bladder (15/50, 30% of cases).

Discussion

Lymphomas of the gallbladder and extrahepatic bile ducts are exceedingly rare. Of a total of 1452 gall bladder specimens examined over a five-year-period, Darmas et al. found only one case of lymphoma(18). Almost all documented cases of lymphomas at these sites have been case reports and the present study represents the largest series of gall bladder lymphomas to date. The majority of patients with gall bladder lymphoma present with symptoms of cholecystitis. In our series, patients with DLBCL and EMZL were older and were more likely to have gallstones than those with other lymphoma types. Even though the age distribution is likely to be skewed by the presence of unusual lymphoma variants occurring in immunocompromised hosts, all the patients with DLBCL and EMZL were older than 70 years of age.

It is notable that the spectrum of gall bladder lymphomas mirrors the spectrum of lymphomas observed in the gastrointestinal tract. In our study, the most common lymphoma types were DLBCL, EMZL, FL, B-LBL with additional instances of extracavitary PEL and PBL, all subtypes that may present with gastric or intestinal mucosal disease. When our cases are taken in combination with those reported in literature, the most common lymphoma types in the gall bladder/bile ducts are DLBCL and EMZL (16/66, 24% each) followed by FL (10/66, 15%) and LBL (4/66, 6%). Comparative clinical features for these subtypes are shown in Table 5. Primary lymphoma of the extrahepatic bile ducts is even more uncommon than gall bladder lymphoma. We encountered only one case of bile duct lymphoma, adding to the 16 previously reported cases. Bile duct lymphomas probably cause a clinically significant obstruction to bile flow, possibly resulting in patients presenting earlier and with less frequent nodal involvement.

Similar to EMZL of other anatomic sites, those in the gall bladder show a female preponderance. As in other sites, one can postulate that acquired mucosa associated lymphoid tissue (MALT) secondary to infection or chronic inflammation may produce the substrate for these lymphomas(30). In support of this hypothesis, Tomori et al have reported that although the gall bladder normally has sparse lymphoid tissue, MALT may develop in 11% of gallbladders in association with positive bile cultures and gallstones(65). On the other hand, Angelopoulou et al hypothesize that in EMZL, the malignant transformation of the original clone could have occurred outside the gall bladder with subsequent homing via an adhesion molecule mechanism(3). Their hypothesis is supported by a recent report of sequential development of a low grade MALT lymphoma affecting the stomach, the small intestine and the gallbladder eight and three years apart, respectively(59). Tumor cells from all three sites were shown to derive from a single clone by the demonstration of an identical immunoglobulin heavy chain gene rearrangement using the polymerase chain reaction technique. Genetic studies in one case showed a gall bladder EMZL to have the *BIRC3/MALT1* translocation that is most often associated with gastric EMZL(7).

In general, DLBCL is the most common type of extranodal lymphoma. In the gallbladder/bile ducts, DLBCL occurs at a mean age of 60 years, without gender preference and is more likely than the other subtypes to be associated with gallstones and regional lymph node involvement. Gall bladder DLBCL has been postulated to evolve from follicular cholecystitis and low grade MALT lymphomas(43). Although this is a possible explanation of lymphomagenesis at this site, our cases with DLBCL were younger than those with EMZL, and had different clinicopathologic features suggesting that these DLBCLs were more likely to be *de novo* tumors rather than evolved from EMZL. In addition, we encountered a single case of FL, Grade

3B, a tumor that is felt to be biologically closely related to DLBCL, and typically lacks both BCL2 protein and the *BCL2/IGH@* translocation(8).

Extranodal variants of DLBCL that we report for the first time in the gall bladder include PBL and PEL. Both PBL and PEL typically affect HIV-positive patients, as was true in our cases. The former most commonly involves the oral cavity(17), although involvement of other mucosal sites, bone and soft tissue is often seen(20). PEL usually presents with body cavity effusions without detectable mass lesions. However, the gastrointestinal tract is one of the more common sites of extracavitary PEL, and progression to positive effusions is not always seen (11,12,19). Our patient presented with an isolated gallbladder mass composed of large cells that expressed MUM1, EMA, HHV8 (LANA), EBER and CD3 (cytoplasmic). Aberrant expression of CD3 has been reported previously in instances of PEL, as well as other EBV-positive large B-cell lymphomas(27,50). In addition to the cases of PEL and PBL, two cases of angiotropic lymphoma were reported in literature (37,38) and occurred in older individuals.

Primary FL of the intestine differs clinically from primary nodal FL and was recognized in the 2008 WHO classification as a separate subtype(61). The duodenum is the most commonly affected site(52,73). Similar to duodenal FL, we identified one case involving the gallbladder that presented as an isolated polypoid lesion with localized mucosal disease without evidence of systemic involvement. The single case of MCL also affected the gall bladder in a pattern similar to lymphomatous polyposis of the intestine and represents the first documentation of this lymphoma subtype at this site. Although the neoplastic cells expressed cyclin D1 and SOX11, the tumor cells were negative for CD5, an uncommon feature in mantle cell lymphoma, sometimes associated with indolent disease(23). Our case of MCL had disease limited to the mantle zones, surrounding residual reactive germinal centers, and conforms to what has been termed *in situ* MCL(4,55).

There were two cases of B-LBL. B-LBL is more likely than T-LBL to present with disease outside of the hematolymphoid organs(39). In a large study of 25 cases of precursor B-LBL without leukemic involvement, Lin et al. identified bone, soft tissue, and skin as the most commonly involved sites, but two cases involved the gastrointestinal tract(39). In addition to our two cases, there has been one previous report each of B-LBL(25) and T-LBL(44) involving the gall bladder. None of the four cases had an associated gallstone or regional lymph node disease.

Secondary involvement of the gall bladder in a systemic lymphoma is also rare; in a review of 1269 cases, the gallbladder was secondarily invaded in only 30 (2.4%) cases(56). In the present study, five patients with systemic lymphoma initially presented with gallbladder disease. One patient had classical Hodgkin lymphoma, while others had various forms of B-cell lymphoma. Histologically, all five cases showed transmural involvement, similar to most of the cases with primary gallbladder lymphoma, suggesting that histological pattern of gallbladder involvement may not help differentiate primary and secondary lymphomas at this site.

In summary, we have detailed the clinicopathological spectrum of primary lymphomas of the gallbladder and extrahepatic bile ducts based on an analysis of 14 cases from our files and a review of 52 cases reported in literature. Gall bladder lymphomas present with non-specific features of cholecystitis, whereas obstructive jaundice is more likely with bile duct disease. In general, these lymphomas appear to recapitulate the spectrum of extranodal lymphomas affecting the gastrointestinal tract, with a predominance of DLBCL, EMZL, and FL, particularly of the primary intestinal or duodenal type. Although the inclusion of a number of rare entities in our series, including *in-situ* MCL, PBL and solid PEL, relates to the nature of our consultation practice, these subtypes also have been reported to occur in the intestine. The very broad spectrum of disease types encountered underscores the need for detailed

immunophenotypic analysis of gall bladder lymphocytic infiltrates for accurate diagnosis and management.

Acknowledgments

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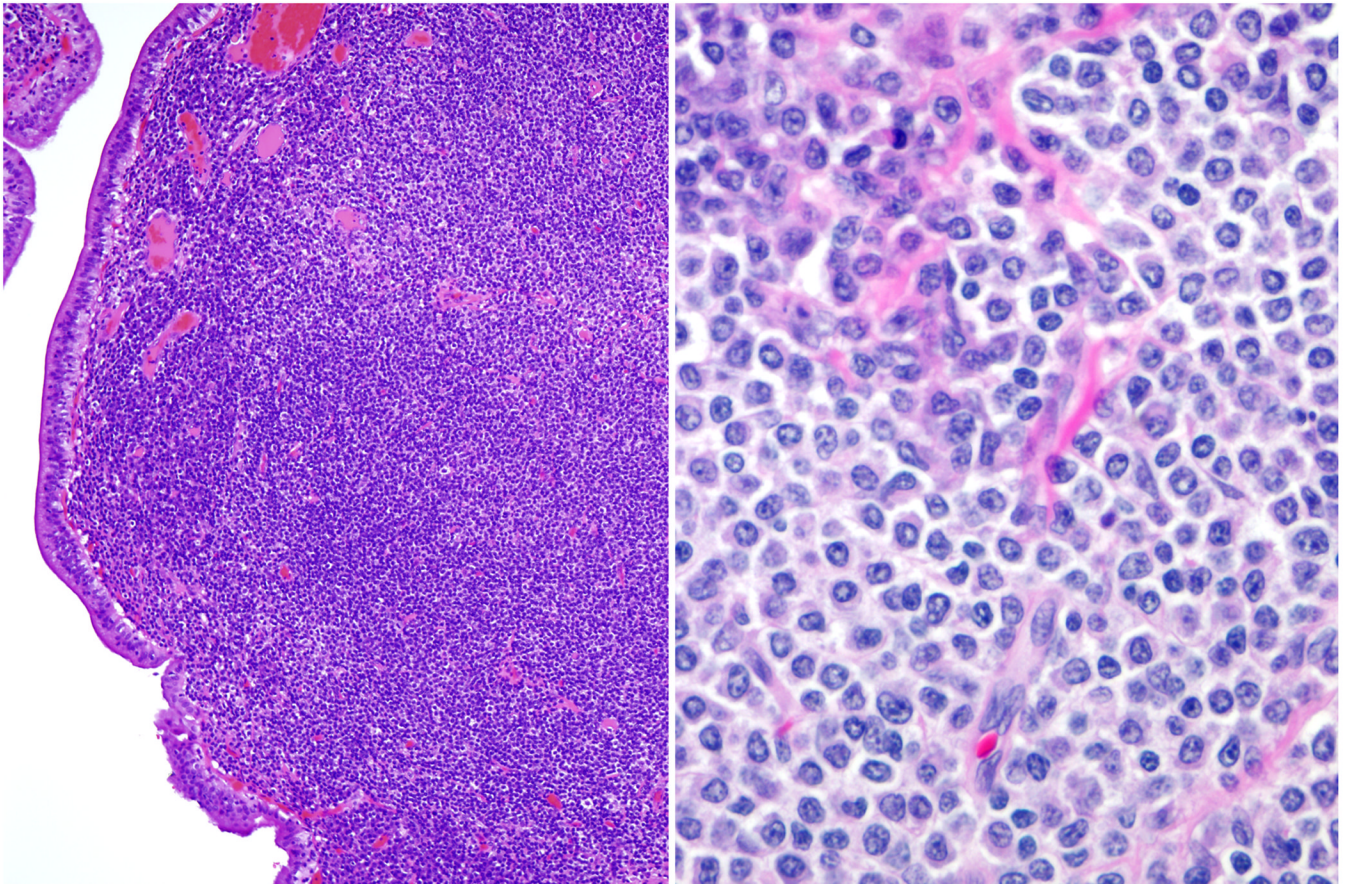
Fig. 1. Extranodal marginal zone lymphoma
A. The gall bladder mucosa is involved by a dense lymphoid infiltrate. **B.** Many cells exhibit plasmacytoid differentiation whereas others have a rim of pale cytoplasm and a monocytoid appearance.
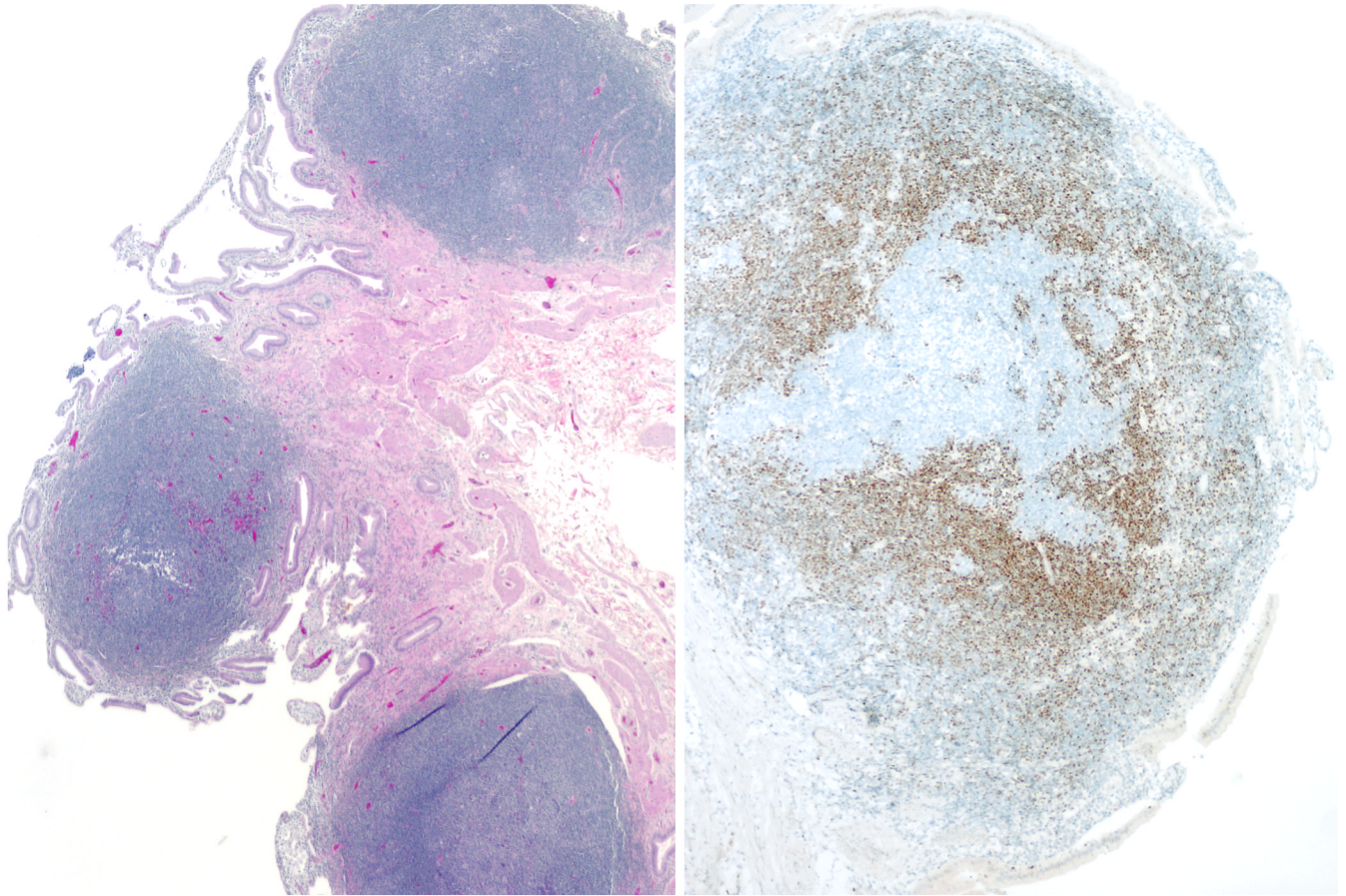
Fig. 2. Mantle cell lymphoma with features of lymphomatous polyposis
A. A polypoid infiltrate is present within the gall bladder mucosa. **B.** Cyclin D1 immunostain highlights the neoplastic cells, which are largely confined to the mantle zones surrounding negative reactive germinal centers.
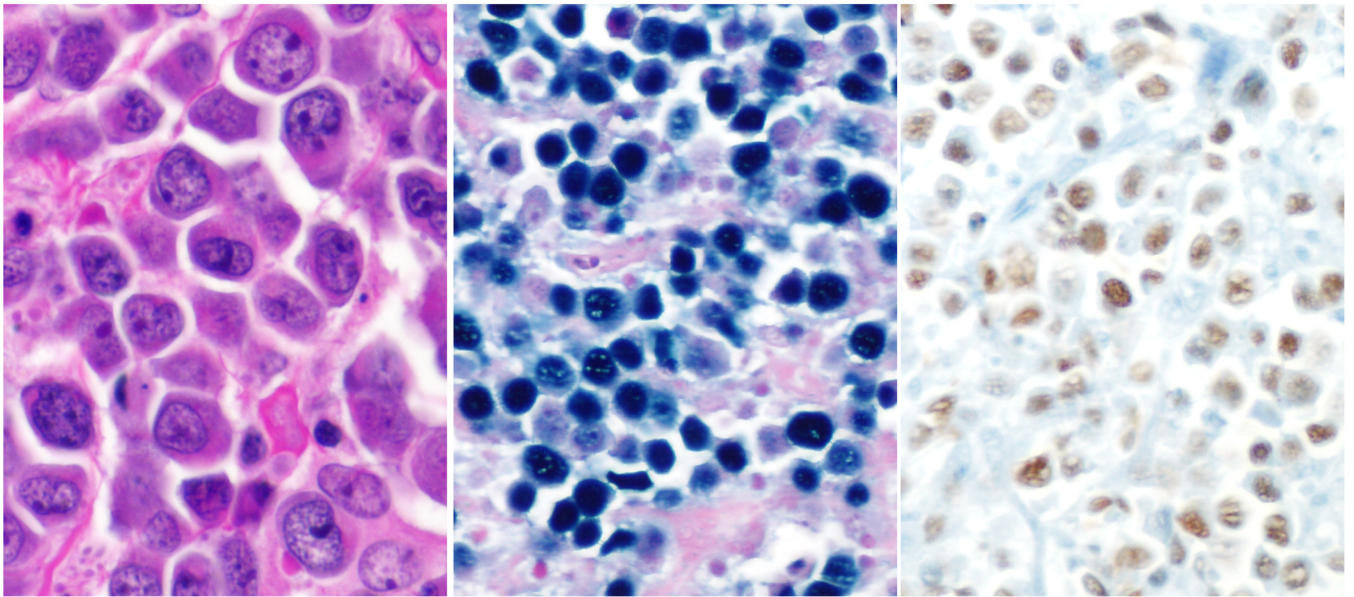
Fig. 3. Extracavitary variant of primary effusion lymphoma
A. The cells are large and pleomorphic with ample cytoplasm and prominent central eosinophilic nucleoli. **B.** In-situ hybridization for EBV (EBER probe) and **C.** HHV-8 immunostain shows positivity in nuclei of neoplastic cells.
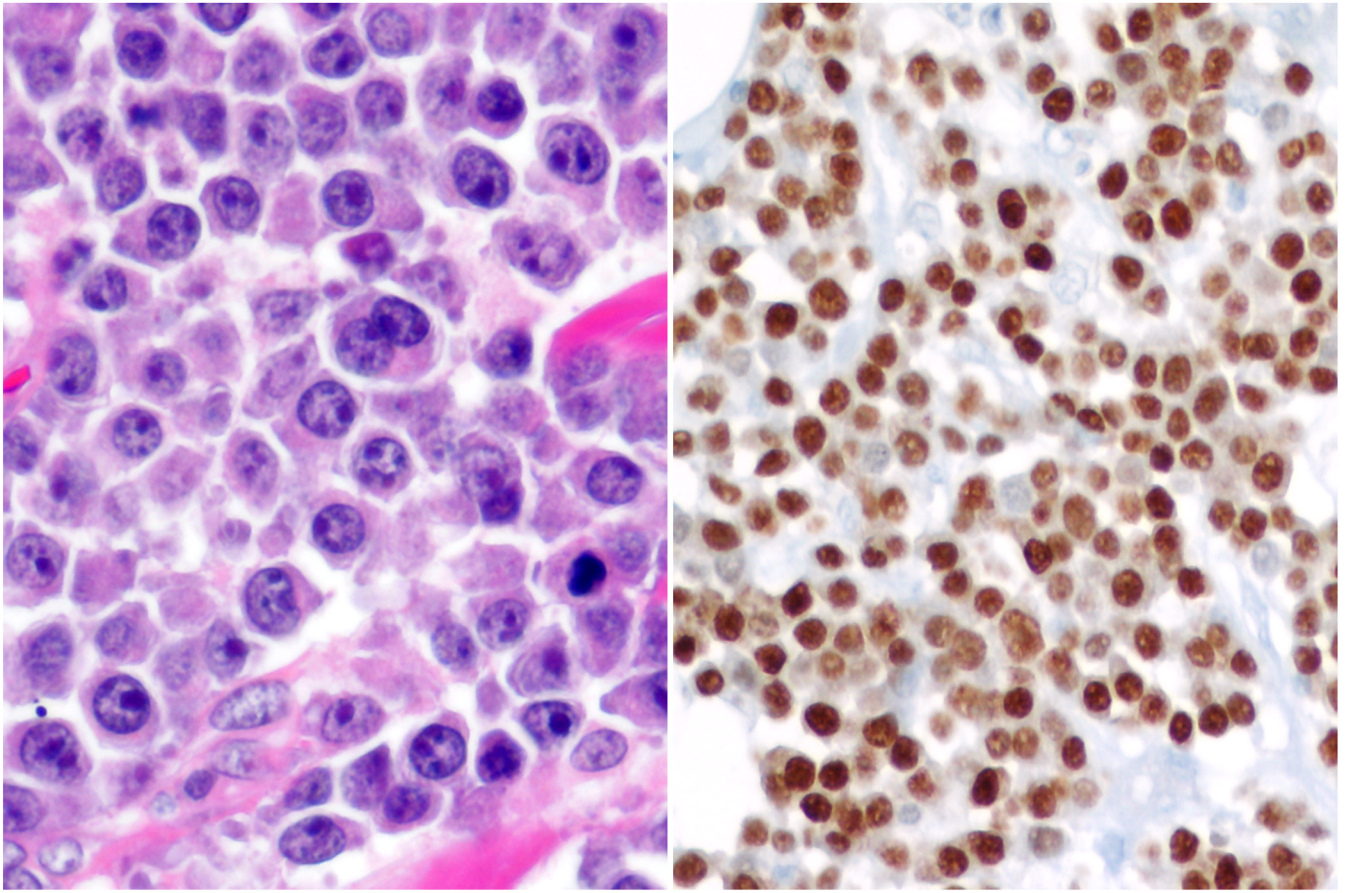
Fig. 4. Plasmablastic lymphoma
A. There is a monomorphic infiltrate of cells with enlarged nuclei, prominent nucleoli and moderate amount of eosinophilic cytoplasm. **B.** Neoplastic cells are strongly and diffusely positive for MUM-1/IRF-4.

Table 1

Clinicopathologic Features of Primary Gall Bladder and Bile Duct Lymphomas.

Case/Sex	Age	Clinical presentation	Stones	Diagnosis	Regional node involvement	Pertinent studies
1/M	5	Cholecystitis	No	PTCL (PTLD)	Yes	CD2+, CD4+, CD8−, BF1+, CD56−, EBER−, TRG monoclonal
2/F	37	Cholecystitis	No	B-LBL	NA	CD79a+, PAX5+, CD10+, TdT+, CD20(focal)
3/M	37	GB mass HIV+	No	PEL, Extracavitary variant	No	PAX5+ (focal), MUM1+, EMA+, EBER+, HHV8+
*4/F	48	Obstructive jaundice	No	FL Grade 3B	No	CD20+, CD30+, CD43+ (focal), BCL2−, BCL6−, CD10−
5/M	51	Cholecystitis and GB mass, HIV+	No	PBL	NA	CD79a+, CD138+, MUM1+, CD10+(focal), EBER+
6/M	51	NA	NA	FL Grade 1–2	No	CD20+, CD10+, BCL2+, BCL6+
7/M	51	Cholelithiasis	Yes	FL Grade 1–2	Yes	CD20+, CD10+, BCL2+
8/M	65	Incidental cholecystectomy; colon resection for adenocarcinoma	No	MCL in situ	NA	CD20+, CD5−, CD43+, SOX11+, CYCLIN D1+, LAMBDA+ t(11;14)+
9/M	72	Cholecystitis	Yes	DLBCL	Yes	CD20+, CD10+, BCL2+, t(14;18)+
10/M	74	Cholelithiasis, h/o colon cancer	Yes	EMZL	NA	CD20+(focal), CD79a+, KAPPA+, CD43−, IGH monoclonal
11/F	74	Cholecystitis	No	DLBCL	NA	CD20+, CD10−, BCL6+, MUM1−, BCL2+
12/M	74	Cholecystitis	No	B-LBL	No	PAX5+, CD10+, CD99+, TdT+(focal), IGH monoclonal
13/M	75	Cholecystitis	Yes	DLBCL	NA	CD20+, CD10−, BCL6−, BCL2+
14/F	84	Cholecystitis	No	EMZL	NA	CD20+, CD79a+, KAPPA+ (focal), IGH

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Case/Sex	Age	Clinical presentation	Stones	Diagnosis	Regional node involvement	Pertinent studies
						monoclonal

*
case involving common hepatic duct, previously reported by Jho et al (32)

DLBCL – diffuse large B-cell lymphoma; EMZL – extranodal marginal zone lymphoma; FL – follicular lymphoma; GB – gall bladder; LBL – lymphoblastic lymphoma; MCL – mantle cell lymphoma; NA – not available; PBL – plasmablastic lymphoma; PEL – primary effusion lymphoma; PTCL – peripheral T-cell lymphoma; PTLD – post-transplantation lymphoproliferative disorder

Table 2

Systemic Lymphomas Presenting With Gall Bladder Disease

Case/Sex	Age	Clinical presentation	Stones	Diagnosis	Pertinent studies
1/M	38	Gallbladder mass	No	TCHRBCL	CD20+, CD30−, BCL6+, EBER−
2/F	59	Abdominal lymphadenopathy	Yes	DLBCL	CD20+, BCL2+, t(14;18)+, t(8;14)+
3/F	60	Lymphadenopathy	No	B-NHL	CD20+, BCL6+, EBER+, IGH monoclonal
4/F	82	Incidental cholecystectomy	NA	MCCHL	CD30+, CD15+ (weakly), EBER+
5/M	85	Cholecystitis	No	EBV+ DLBCL of the elderly	CD20+(focal), CD30+(focal), EBER+

DLBCL – diffuse large B-cell lymphoma; MCCHL – mixed cellularity classical Hodgkin lymphoma; NA – not available; NHL – non-Hodgkin lymphoma; TCHRBCL – T-cell histiocyte rich large B-cell lymphoma

Table 3

Primary Gall Bladder Lymphomas Reported in Literature

Diagnosis	No. of cases	Age range (mean)	Gender	Gall stones	Regional adenopathy	References
EMZL*	13	31–91 (68)	11F, 2M	6/11, 2NA	2/10, 3NA	(6,35) (66) (53) (51) (62) (45) (43) (14) (7) (1) (49) (29)
DLBCL**	9	40–78 (63.7)	4F, 5M	5/6, 3 NA	2/7, 1NA	(51,57) (72) (70) (28,34) (13) (24) (67)
LGBCL	1	75	F	1/1	NA	(18)
FL	4	63–78 (71)	3F, 1M	2/4	1/4	(47,69) (22) (31)
B-LBL	1	4	M	0/1	0/1	(25)
T-LBL	1	26	F	0/1	0/1	(44)
PDLL	1	54	M	0/1	1/1	(9)
Angiotropic	1	68	F	1/1	NA	(38)
Intravascular	1	79	M	0/1	0/1	(37)
Lymphosarcoma	2	44, 75	2F	1/2	2/2	(68)
Reticulum cell sarcoma	1	29	M	0/1	NA	(71)
MCCHL	1	75	M	1/1	0/1	(48)

*
Includes a "pseudolymphoma" (29)

**
Includes a "diffuse mixed small and large cell NHL" (67)

DLBCL – diffuse large B-cell lymphoma; EMZL – extranodal marginal zone lymphoma; FL – follicular lymphoma; LBL – lymphoblastic lymphoma; LGBCL – low grade B-cell lymphoma; MCCHL – mixed cellularity classical Hodgkin lymphoma; NA – not available; NED – no evidence of disease; PDLL – poorly differentiated lymphocytic lymphoma

Table 4

Primary Extrahepatic Bile Duct Lymphomas Reported in Literature

Diagnosis	No. of cases	Age range (mean)	Gender	Gall stones	Regional adenopathy	References
DLBCL and other aggressive B-NHLs*	7	34 – 68 (49)	4F, 3M	1/4, 3NA	1/6, 1NA	(33,36) (41,63) (41) (46) (21) (10)
FL	4	33 – 53 (43)	3F, 1M	0/1, 3NA	0/4	(16,60) (2) (40)
EBV-PTLD	2	41, 59	1F, 1M	NA	0/2	(5)
EMZL	1	59	M	NA	0/1	(58)
T-NHL, NOS	1	25	F	NA	0/1	(15)
NHL, NOS	1	48	M	NA	0/1	(64)

*Includes one T-cell histiocyte rich large B-cell lymphoma (10)

DLBCL – diffuse large B-cell lymphoma; FL – follicular lymphoma; EBV-PTLD – EBV-related post-transplantation lymphoproliferative disorder; EMZL – extranodal marginal zone lymphoma; NA – not available; NHL – non-Hodgkin lymphoma; TCHRBCL –

Table 5

Comparison of Clinicopathologic Features of Most Common Subtypes

Type	No (%)	Mean Age	M:F	Symptomatic	EHBD disease	Stones	Node +
EMZL	16 (24%)	68.8	4:12	14/15, 93%	2/16[#], 12.5%	7/13, 54%	2/11, 18%
DLBCL[*]	16 (24%)	60.4	8:8	12/15, 80%	6/16, 37.5%	8/12, 66%	4/12, 33%
FL	10 (15%)	56.5	4:6	8/9, 89%	4/10, 40%	3/7, 43%	2/10, 20%
LBL	4 (6%)	35.3	2:2	4/4, 100%	0/4, 0%	0/4, 0%	0/3, 0%

[#] One case involved both gallbladder and common bile duct

[*] Includes one case of T-cell histiocyte rich large B-cell lymphoma

DLBCL – diffuse large B-cell lymphoma; EHBD – extrahepatic bile duct; EMZL – extranodal marginal zone lymphoma; FL – follicular lymphoma; LBL – lymphoblastic lymphoma