# An unusual case of primary extranodal lymphoma of the gallbladder

**Roberto Pezzuto,[1] Davide Di Mauro,[1] Luca Bonomo,[1] Amita Patel,[2] Edoardo Ricciardi,[1] Andrea Attanasio,[1] Antonio Manzelli[1]**

**Departments of [1]Upper Gastrointestinal Service and [2]Cellular Pathology, Royal Devon and Exeter Hospital, UK**

## Abstract

Primary gallbladder lymphoma is an extremely rare disease. We report a case of a 63 year-old woman who has been admitted with gradual onset abdominal pain in the upper right quadrant and in the suprapubic region, nausea and malaise. According to the computed tomography scan of the abdomen, which was suggestive of chronic cholecystitis, she was treated conservatively. A laparoscopic cholecystectomy was performed 5 months later and the histological examination of the gallbladder showed a low grade small lymphocytic lymphoma. The patient has been taken over by the hematology team who kept her under surveillance as no further treatment was deemed as necessary. The purpose of this paper is to report a rare case of primary gallbladder lymphoma and to demonstrate that a laparoscopic cholecystectomy may be a valid treatment for this disease.

## Introduction

Non-Hodgkin lymphomas (NHL) are a spectrum of neoplastic diseases arising from lymphatic germ lines. Twenty to forty percent of NHLs occur primarily in extranodal tissues.[1] The definition of primary extranodal lymphoma remains a controversial issue and the different definitions impact on incidence and prognosis.[2-4] Most of them originates from the gastrointestinal tract, but other common sites are skin, orbit and salivary glands; less frequently they have been found in the lung, thymus, breast, brain, bone and soft tissue.[5,6] We report a rare case of primary extranodal NHL of the gallbladder.

## Case Report

A 63 year-old Caucasian woman presented to the emergency department at Wonford Hospital, Exeter, UK, with gradual onset abdominal pain in the upper right quadrant and in the suprapubic region, nausea and malaise. Her past medical history was of a single episode of sigmoid diverticulitis, which was treated conservatively, and she was not on regular medications. On presentation her vital signs were within the normal range and she had no fever. Physical examination showed soft abdomen with right upper quadrant tenderness and Murphy's sign.

Laboratory blood tests revealed a normal white cells count ($10.9\times10^9$/L) and mildly raised C-reactive protein (54 mg/L), while renal and liver function parameters were within the normal range. Computed tomography (CT) scan of the abdomen showed a thick-walled gallbladder containing large calcified stones, suggestive of chronic cholecystitis. Both the intrahepatic and extrahepatic biliary ducts were not dilated.

Symptoms improved promptly with intravenous antibiotics and the patient was discharged home after five days with a three days course of oral antibiotics.

An elective laparoscopic cholecystectomy was performed five months later. The intraoperative findings were of grossly inflamed thick walled gallbladder, and dense adhesions between the greater omentum, the liver and the gallbladder. The patient was sent home the same day of surgery and the following postoperative course was uneventful.

Routine histological examination of the gallbladder showed findings in keeping with a low grade small lymphocytic lymphoma (SLL/CLL).

The macroscopical examination revealed several stones up to 15 mm diameter in the gallbladder, which measured 70×30×20 mm. The mucosa was focally pale, partly inflamed and the wall up to 4 mm thick (Figure1).

Microscopic examination found out a thickened gallbladder wall with denuded surface and a dense underlying follicular lymphoid population which abutted the serosa. No mucosal involvement is seen. These follicles infiltrated into adipose tissue in places. Focal xanthogranulomatous inflammation was also seen (Figure 2).

There was an underlying CD21 positive follicular architecture with a mainly perifollicular distribution of small round lymphocytes with occasional blasts and a few plasma cells. This population showed positive reactivity with CD20, CD79a, CD23 and BCL2, although CD5 and BCL6 were negative. IgM positivity with weak IgD positivity and Kappa restriction was also evident. MIB proliferation index was low (approximately 5%). The cystic duct lymph node retrieved has not been examined with immunohistochemistry (Figure 3).

In conclusion, all the features were in favor of SLL/CLL (low grade non-Hodgkin's lymphoma).

As per the multidisciplinary team meeting discussion, the patient underwent staging CT of the neck, thorax, abdomen and pelvis, which did not show any evidence of lymphomatous dissemination. The patient then had been taken over by the hematology team who kept her under surveillance as no further treatment was deemed as necessary.

## Discussion and Conclusions

Primary NHL of the gallbladder, defined as a disease confined in the gallbladder with or without involvement of contiguous lymph nodes is uncommon and less than 50 cases have been reported in literature. The first report appeared in English medical literature in 1971. Yasuma *et al.*[7] reviewed 93 cases of primary sarcoma of the gallbladder. Eight of these were NHL (4

Correspondence: Andrea Attanasio, Upper GI Department, Royal Devon and Exeter Foundation Trust, Barrack Road, Exeter EX2 5DW, UK.
Tel.: +39.3392243551.
E-mail: attanasio.andrea.student@gmail.com

Key words: Lymphoma; Gallbladder; Laparoscopic Cholecystectomy.

Contributions: RP was the major contributor in writing the manuscript; AP performed the histological examination of the gallbladder; AM performed the laparoscopic cholecystectomy and was responsible for scientific revision; DDM, LB, ER were involved in clinical management of the patient and interpretation of data; AA is the corresponding author and contributed to write the paper.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 15 November 2016.
Revision received: 22 December 2016.
Accepted for publication: 28 December 2016.


*Hematology Reports 2017; 9:6972*
*doi:10.4081/hr.2017.6972*

lymphocytic lymphomas and 4 reticulum cell lymphomas, respectively). Darmas *et al*.,[8] described only one case of gallbladder NHL out of a total of 1452 histopathological examination of routine cholecystectomy specimens.

According to the last World Health Organization (WHO) classification (2016),[9] the spectrum of lymphomas observed in the gallbladder reflects that of gastrointestinal tract lymphomas, with predominance of mucosa associated lymphoid tissue (MALT) type and diffuse large B cells type (DLBL).[10] Primary MALT is the most common lymphoma of gastrointestinal tract.[5] It has been suggested that MALT lymphomas of the gallbladder may occur in the context of chronic cholecystitis with cholelithiasis or bacterial infection. The mechanism based on the chronic inflammatory process would be similar to that described previously in the stomach (*Helicobacter pylori* infection) and conjunctiva.[11-13] The continuous antigenic stimulus may cause chromosomal translocation which results in antigenic-independent proliferation.[14] Bisig *et al.*[15] have described a case of gallbladder MALT lymphoma with t(11;18) (q21; q21) similar to that seen in the stomach. MALT is an indolent lymphoma with a low grade of malignancy.[9] It mainly occurs in women and,[10] if localized in the gallbladder only, cholecystectomy alone is considered curative with an excellent prognosis in the majority of the cases.[16]

DLBL is the most common type of primary extranodal NHL.[5,6] It's an aggressive form with a high grade of malignancy, showing a marked tendency to systemic dissemination.[9] It commonly occurs in the brain and spinal cord (CNS), eye, thyroid, Waldeyer's ring, breast, liver and genitourinary tract.[5,6] McCluggage *et al*.[17] suggest that DLBL of gallbladder may be a malignant evolution of MALT lymphoma. However Mani *et al*.[10] state that DLBCL of gallbladder is a *de novo* tumor, with different clinical and histo-pathologic features and a younger onset age.

Follicular lymphoma type is the third most common primary lymphoma of the gallbladder,[10] although it tends to occur more frequently in the duodenum.[18] Less than 10 cases have been described in the literature and it has been regarded as a slow progression disease.[9]

Other types of lymphoma include the B-lymphoblastic, T-lymphoblastic, angiotropic or intravascular, low grade B-cell, poorly differentiated lymphocitic, lymphosarcoma and reticulum cell sarcoma.[10]

To the best of the authors' knowledge, no case of primary SLL/CLL of the gallbladder has been reported in literature so far. According to De Rossi *et al*.,[19] CD5-negative B-CLL can be considered as an infrequent subtype of B-CLL, 7 to 20%,[20] as no significant differences have been observed in terms of clinical features and response to the conventional therapy.

Patients with primary gallbladder lymphoma usually present with long standing mild right upper quadrant pain or onset of biliary colic or thorough signs of cholecystitis.[21] The radiological features of gallbladder lymphoma depend on the hystopathological types: high-grade lymphomas, such as DLBL, have a tendency to form a solid and large mass in the gallbladder or may present with marked and irregular gallblad-

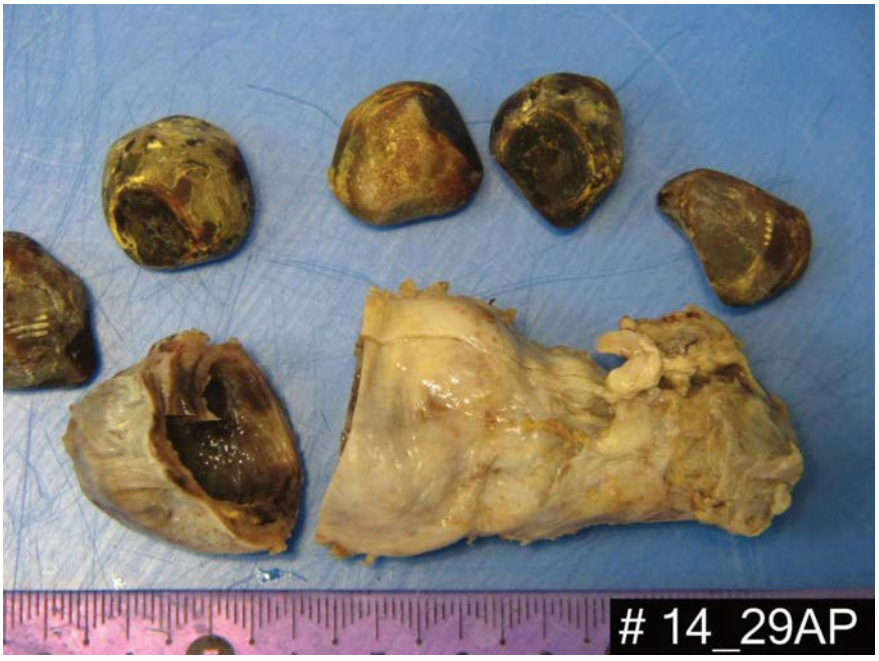


**Figure 1. Gallbladder 70×30×20 mm, containing several stones up to 15 mm diameter. Mucosa is partly pale, partly inflamed. Wall up to 4 mm thick.**

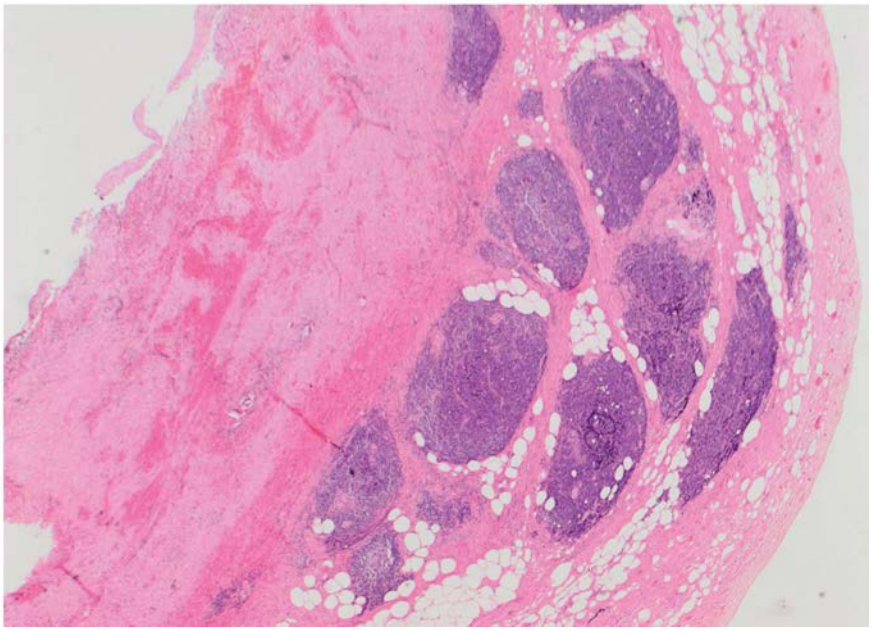

**Figure 2. Gallbladder wall with denuded surface and a dense underlying follicular lymphoid population which abuts the external surface. These follicles infiltrate into adipose tissue in places. Focal xanthogranulomatous inflammation is seen.**

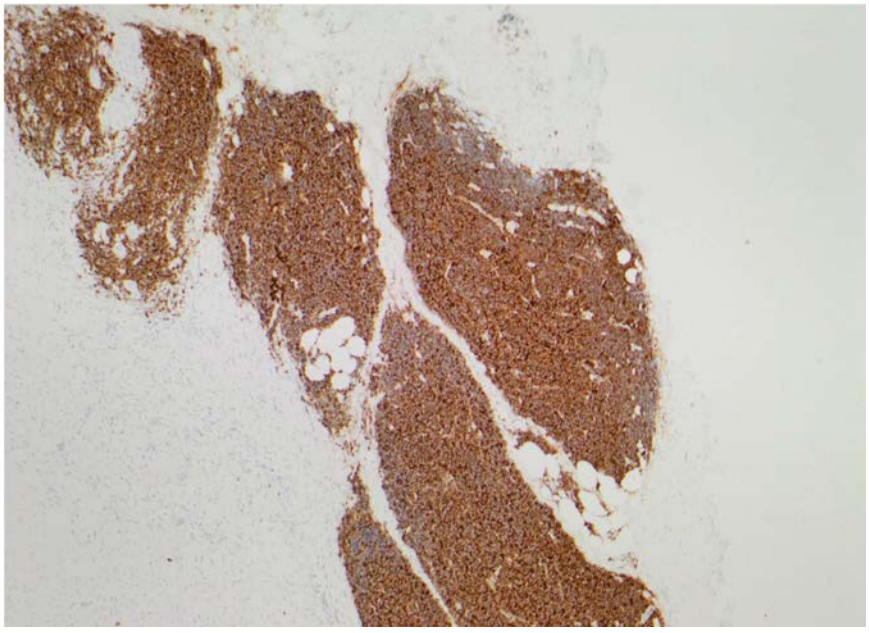

**Figure 3. Bcl2 and CD20 positive immunohistochemistry amidst the lymphoma cell clusters within fat.**

der wall thickening, whilst most of the low-grade lymphomas, such as MALT, follicular lymphomas or as in the case we presented, SLL/CLL, show mild thickening of the gallbladder wall.[22]

However, preoperative diagnosis is rare and in the majority of the cases, is made after surgery with histo-immunological study.[23,24] Gallstones are present up to 40% of cases and regional lymph nodes involvement has been noted in 30% of patients while local contiguous invasion of surrounding tissues is rather rare.[10,23] On pathology examination the mucosa is intact.[22]

In conclusion primary lymphoma of the gallbladder is an exceedingly rare condition, but it should be added to differential diagnosis of gallbladder mass in addition to carcinoma and metastases. Although rare, the authors feel such a case may support the arguments in favor of the routine histological examination of gallbladder specimens.

## References


1. Krol DG, le Cessie S, S. Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Ann Oncol 2003;14:131-9.
2. Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Br J Surg 1961;49:80-9.
3. Kramer MHH, Hermans J, Wijburg E, et al. Clinical relevance of BCL2, BCL6, and MYC rearrangements in diffuse large B-cell lymphoma. Blood 1998;92:3152-62.
4. Kramer MH, Hermans J, Parker J, et al. Clinical significance of bcl2 and p53 protein expression in diffuse large B-cell lymphoma: a population-based study. J Clin Oncol 1996;14:2131-8.
5. Zucca E, Roggero E, Bertoni F, Cavalli F Primary extranodal non-Hodgkin's lymphomas. Part 1: Gastrointestinal, cutaneous and genitourinary lymphomas. Ann Oncol 1997;8:727-37.
6. Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 2: Head and neck, central nervous system and other less common sites. Ann Oncol 1999;10:1023-33.
7. Yasuma T, Yanaka M. Primary sarcoma of the gallbladder: report of three cases. Acta Pathol Jpn 1971;21:285-304.
8. Darmas B, Mahmud S, Abbas A, et al. Is there any justification for the routine histological examination of straightforward cholecystectomy specimens? Ann R Coll Surg Engl 2007;89:238-41.
9. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
10. Haresh M, Fina C, Lluís C. Gallbladder and extrahepatic bile duct lymphomas: clinicopathological observations and biological implications. Am J Surg Pathol 2010;34:1277-86.
11. Tomori H, Nagahama M, Miyazato H. Mucosa-associated lymphoid tissue (MALT) of the gallbladder: a clinicopathological correlation. Int Surg 1999;84:144-50.
12. Parsonnet J, Hansen S, Rodriguez L. Helicobacter pylori infection and gastric lymphoma. N Engl J Med 1994;330:1267-71.
13. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter on-associated gastritis and primary B-cell gastric lymphoma. Lancet 1991;338:1175-6.
14. Levine EG, Arthur DC, Machinicki J. Four new recurring traslocation in non-Hodgkin lymphoma. Blood 1989;74;1796-800.
15. Bisig B, Copie-Bergman C, Baia M. Primary mucosa-associated lymphoid tissue lymphoma of the gallbladder: report of a case harbouring API2/MALT1 gene fusion. Hum Pathol 2009;40:1504-9.
16. Koshy M, Zhao F, Garofalo MC. Primary MALT lymphoma of the gallbladder. Case report. J Gastrointestin Liver Dis 2008;17:207-10.
17. McCluggage WG, Mackel E, McCusker G. Primary low grade malignant lymphoma of mucosaassociated lymphoid tissue of gallbladder. Histopathology 1996;29:285-7.
18. Yoshino T1, Miyake K, Ichimura K, Increased incidence of follicular lymphoma in the duodenum. Am J Surg Pathol 2000;24:688-93.
19. De Rossi G, Mauro FR, Lo Coco F, et al. CD5 negative lymphocytosis mimicking typical B-chronic lymphocytic leukaemia. Description of 26 cases. Nouv Rev Fr Hematol 1993;35:451-5.
20. Cartron G, Linassier C, Bremond JL, et al. CD5 negativ B-cell chronic lymphocytic leukemia: clinical and biological features of 42 cases. Leuk Lymphoma 1998;31:209-16.
21. Huang WT, Chuang SS, Huang CC. Primary diffuse large B-cell lymphoma of the gallbladder with cholelithiasis masquerading as acute cholecystitis: case report and literature review. N Z Med J 2007;120:U2470.
22. Ono A, Tanoue S, Yamada Y. Primary malignant lymphoma of the gallbladder: a case report and literature review. Br J

Radiol 2009;82:e15-e19.
23. Imenpour H1, Castagnola M, De Silva G. Incidental finding of peripheral B-cell non-Hodgkin lymphoma, lymphocytic/CLL type, of the gallbladder in a patient with chronic cholecystitis. Pathologica 2011;103:307-10.
24. Bagwan IN1, Ping B, Lavender L, de Sanctis S. Incidental presentation of gallblader MALT lymphoma. J Gastrointest Cancer 2011;42:61-4.
25. Wan-Ting H, Shih-Sung C, Chao-Cheng H. Primary diffuse large B-cell lymphoma of the gallbladder with cholelithiasis masquerading as acute cholecystitis: case report and literature review. J N Z Med Assoc 2007;120: 1251.