An unusual case of primary extranodal lymphoma of the gallbladder

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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 ($10.9 \times 10^9/L$) 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 $70 \times 30 \times 20$ mm. The mucosa was focally pale, partly inflamed and the wall up to 4 mm thick (Figure 1).

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 (approx-

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mately 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

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 lymphocytic, 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 histopathological 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.

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