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Hepatic follicular lymphoma in an old patient with Crohn's disease: a rare case and review of the literature

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Abstract. – OBJECTIVE: Crohn's Disease (CD) has been associated with non-Hodgkin lymphoma. Follicular Lymphoma (FL) limited to the liver is extremely rare, accounting for 1% to 4.4% of all Primary Hepatic Lymphoma (PHL).

CASE PRESENTATION: In 2018, an 85-years old male patient with post-operative recurrence of ileal CD referred rare episodes of fever and mild diffuse abdominal pain. Since cholecystectomy in 2001, clinical history was characterized by recurrent episodes of cholangitis and common bile duct stones. In 2018, ultrasonography and MRI showed a solid focal hepatic lesion (FHL)(4.5 cm x 2.5 cm) in the IV hepatic segment. The radiographic aspect of the lesion was unusual. Initially, focal nodular hyperplasia was suspected. Clinical history of cholangitis and radiological findings subsequently suggested a diagnosis of Hepatic Abscess (HA). A progressive enlargement of the FHL (7.3 cm x 5.8 cm) despite antibiotic treatments, led to perform a liver biopsy. Histological and immunophenotypical analysis of the FHL (7.5 cm x 5.4 cm) enabled a final diagnosis of FL. The "*in situ*" hybridization for Epstein-Barr virus (EBER) was negative. No additional lesions related to FL were initially detected, thus suggesting a very rare case of PHL in an old patient with CD never treated with thiopurines.

CONCLUSIONS: This case report highlights the need to consider a rare diagnosis of FL of the liver in patients showing a challenging focal hepatic lesion of unknown origin.

Key Words:
Crohn's disease, Hepatic follicular lymphoma, Focal lesion, Rare case, Literature review.

Introduction

Crohn's Disease (CD) bears an increased risk of Lymphoproliferative Disorders, more frequently represented by Non-Hodgkin lymphoma (NHL)[1]. Follicular Lymphoma (FL) is the second most frequent B-cell nodal lymphoid malignancy in Western Europe (22% of NHL)[2].

The exclusive hepatic involvement by FL is extremely rare, accounting for 1% to 4.4% of all Primary Hepatic Lymphomas (PHL)[3]. By our knowledge, only 9 cases of FL limited to the liver have been reported[4].

Case Report

In October 2018, an 85 years old caucasian man, with a long (33 years) history of steroid-dependent stricturing ileal CD was assessed during a scheduled outpatient visit. He was a retired clerk, non-smoker, with no family history of CD. The patient appeared in discrete general conditions, complaining rare episodes of mild and diffuse abdominal pain, with associated tenderness, and no other CD-related symptoms. Physical examination of the abdomen revealed a long-lasting indolent mass in the right iliac fossa. Clinical history included an ileo-colonic resection for CD in 1985, related to recurrent obstructions, followed by stricturing post-operative recurrence. Clinical recurrence occurred in 2014, successfully treated with budesonide. Immunomodulators were not given due to advanced age (>80 years) and to steroid-induced remission.

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In 2001, the patient underwent cholecystectomy for lithiasic cholecystistis, followed by common bile duct (CBD) stones complicated by cholangitis. In 2010, CBD stones were endoscopically removed. Comorbidities included asymptomatic Hepatitis C Virus (HCV) infection with HCV-RNA negativity, monoclonal gammopathy and relapsing basal cell carcinomas.

In January 2018, clinical relapses of CD were successfully treated with steroids. In October 2018, abdominal ultrasonography (US) visualized an inhomogeneous liver structure, with a newly diagnosed oval image (5 cm × 4 cm), showing irregular margins and mixed echostructure, including anechoic areas. Aerobilia and dilation of intrahepatic bile ducts (IV hepatic segment) without detectable CBD stones were observed. Abdominal contrast enhanced (c.e.)-Magnetic Resonance Imaging (MRI) showed a solid lesion (4.5 cm × 2.5 cm) in the IV and II hepatic segments, showing a slight c.e. in the arterial phase with mild hypointensity in the portal venous phase and in the delayed phase. MRI findings were inconclusive, although Focal Nodular Hyperplasia (FNH) was suspected.

One month later, abdominal-US revealed an enlargement of the inhomogeneous FHL (6.3 cm x 4.8 cm), together with mobile artifacts related to gaseous material and peripheral vascular signals (Figure 1, panel a).

In December 2018, the patient was hospitalized in relation to the onset of fever associated with weakness and worsened clinical conditions. Abdominal, symptoms were absent. At admission, low grade fever (37.6°C) was recorded. At blood chemistry, no clinically relevant findings were detected (hemoglobin 11.1 g/dL, MCV 86 μ^3, platelets 123/µL, leukocytes 3.33/µL, C-Reactive Protein 16.5 mg/L (n.v. < 5 mg/L), albumin 2.68 g/dL). LDH and oncomarkers were within the normal range. Antibiotic treatments (ceftriaxone and metronidazole) were given. Chest-abdomen c.e.-CT scan (Figure 1, panels b-e) showed the FHL stable in size (6.0 cm × 4.9 cm), isodense in pre-contrast and hypodense in post-contrast images (panels b-d). Pre-papillary choledocholithiasis was also detected (Figure 1, panels b-d). As expected, computed tomography (CT)-scan of the abdomen also visualized an increased bowel wall thickness of the pre-anastomotic ileum related to post-operative recurrence of CD (Figure 1, panel e). Apical fibrotic areas in the right lung, with no enlarged axillary or mediastinal lymph nodes were also identified, as already reported in 2013 by a chest CT-scan (Figure 1, panel l).

Clinical history of cholangitis and radiological findings suggested a diagnosis of Hepatic Abscess (HA). This hypothesis was supported by abdominal c.e.-MRI and cholangio-MRI imaging, visualizing an FHL showing characteristics compatible with an inflammatory/infectious process (Figure 1, panels f-h). Furthermore, 3 additional adjacent areas (20 mm, 8 mm and 17 mm), compatible with small abscesses were also detected. CBD stones confirmed by abdominal-MRI (Figure 1, panel i) were endoscopically removed, followed by patient discharge.

In March 2019, the patient was re-hospitalized due to fever (38°C), chills, weight loss (2 Kg). At abdominal c.e.-CT-scan, an enlargement of the FHL was observed (from 6.0 cm x 4.9 cm to 7.5 cm x 5.4 cm). Therefore, an US-guided biopsy of the FHL was performed. Cultural test of the biopsy specimen was negative. Histopathological and immunohistochemical features of the liver biopsy are shown in Figure 2 (panels a-h). Proliferation of small-medium lymphoid cells similar to indented centrocytes, showing a diffuse growth pattern (CD20+, BCL6+, BCL2+) and substituting the normal parenchyma was detected. Due to a doubtful CD10 negativity, an additional germinal center marker (LMO2) was tested, showing positivity. The B-cell infiltrate was associated with numerous and sparse small T-lymphocytes (CD3+) (Figure 2, panels a-h). Proliferation rate was ~20%, as detected by Ki-67 staining. Isolated Hodgkin-like cells (CD20+, CD30-, CD15-) were present. The absence of both a polymorphic inflammatory background and of small PD1+ T-cells arranged in rosettes around the Hodgkin-like cells, helped to exclude HL. The *in-situ* hybridization for Epstein-Barr virus was negative. These morphologic and immunophenotypic findings allowed a final diagnosis of FL, with diffuse growth pattern and Hodgkin-like cells.

PET-CT scan showed a focal, isolated area of hyperfixation in the left parotid (possible lymph node), and rare mediastinal prevascular and paractracheal lymphadenopathies with a low uptake in the right and left lung hilum (Figure 1, panel m).

Hematologic treatment was delayed due to recurrent pneumonia. Finally, in December 2019, Rituximab (anti-CD20) was given. One month later, the patient deceased due to lobar pneumonia followed by ischemic heart attack.

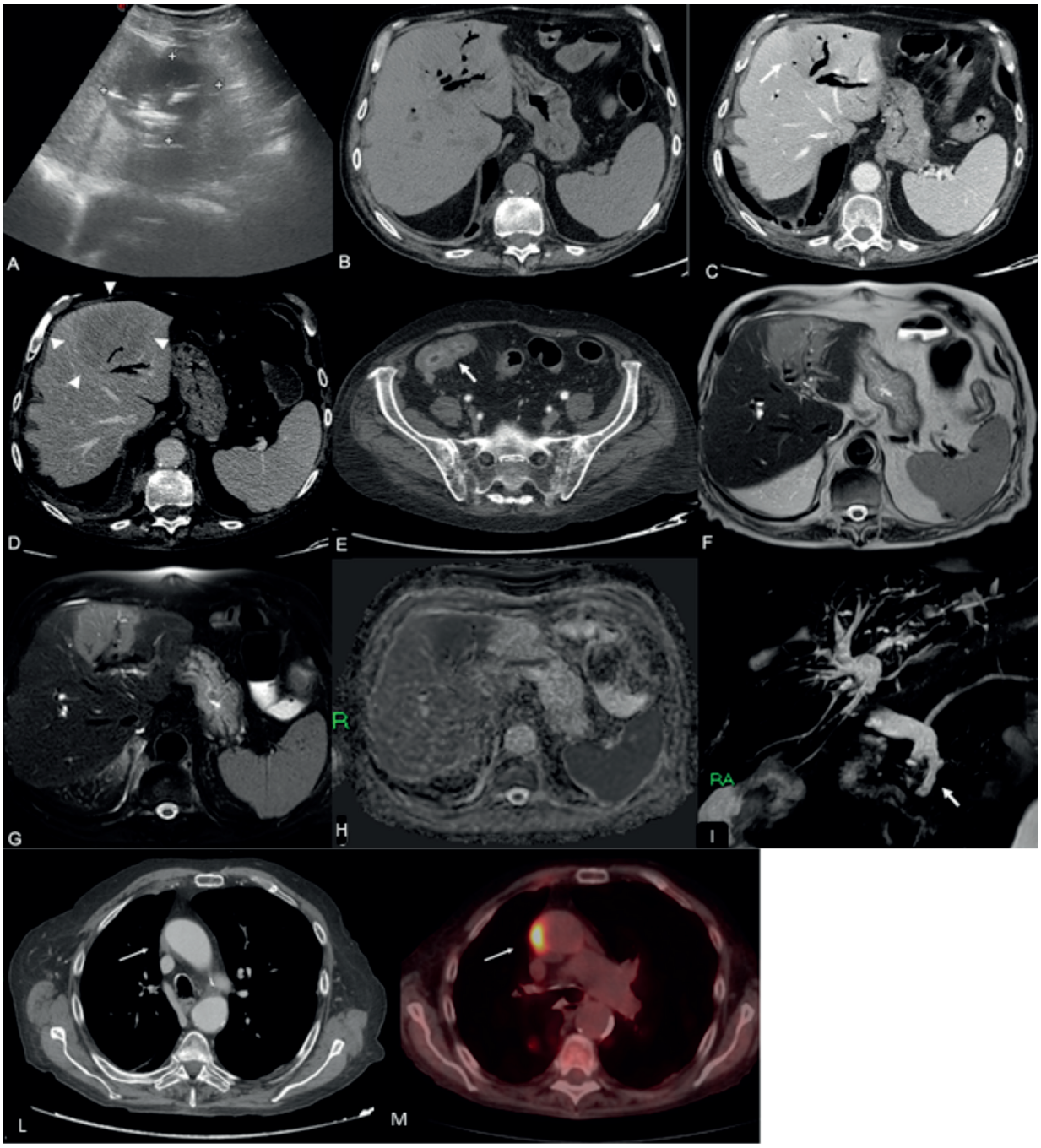

Figure 1. (Panels a-m). Panel a. Ultrasound scan showing in the II, IV, V hepatic segments the presence of a inhomogeneous hypoechoic lesion containing an alternation of anechoic, hypoechoic and hyperechoic mobile artifacts as for the presence of gaseous material (pneumobilia). **Panel b.** Axial CT examination: unenhanced scan demonstrates pneumobilia with isodense hepatic lesion in the IV, III and II segments. **Panels c, d.** Venous (c) and delayed phase (d) Computed Tomography (CT)-scan demonstrates slight hypodensity in the hepatic lesion with regular path of the intrahepatic vessels without signs of stricture-infiltration (arrow and arrowheads). **Panel e.** CT images also visualize an increased bowel thickness of the pre-anastomotic ileum related to post-operative recurrence of CD (arrow). **Panels f-h.** Magnetic Resonance (MR) axial imaging in T2-weighted sequences without (f) and with fat-suppression (g), confirmed the intrahepatic lesion with hyperintense signal. Diffusion weighted imaging with ADC demonstrated restriction of signal (h). **Panel i.** MR-Cholangiopancreatography: coronal image demonstrates choledocholithiasis in pre-papillary region (arrow). **Panel l.** Contrast enhanced chest CT-scan (panel a) in January 2019, visualizing a small, not enlarged para-aortic lymph node (arrow). **Panel m.** CT/PET with FDG performed in May 2019, detecting an enlargement of the para-aortic lymph node, showing an increased size when compared to previous CT imaging, associated with pathological uptake of radiotracer (arrow).

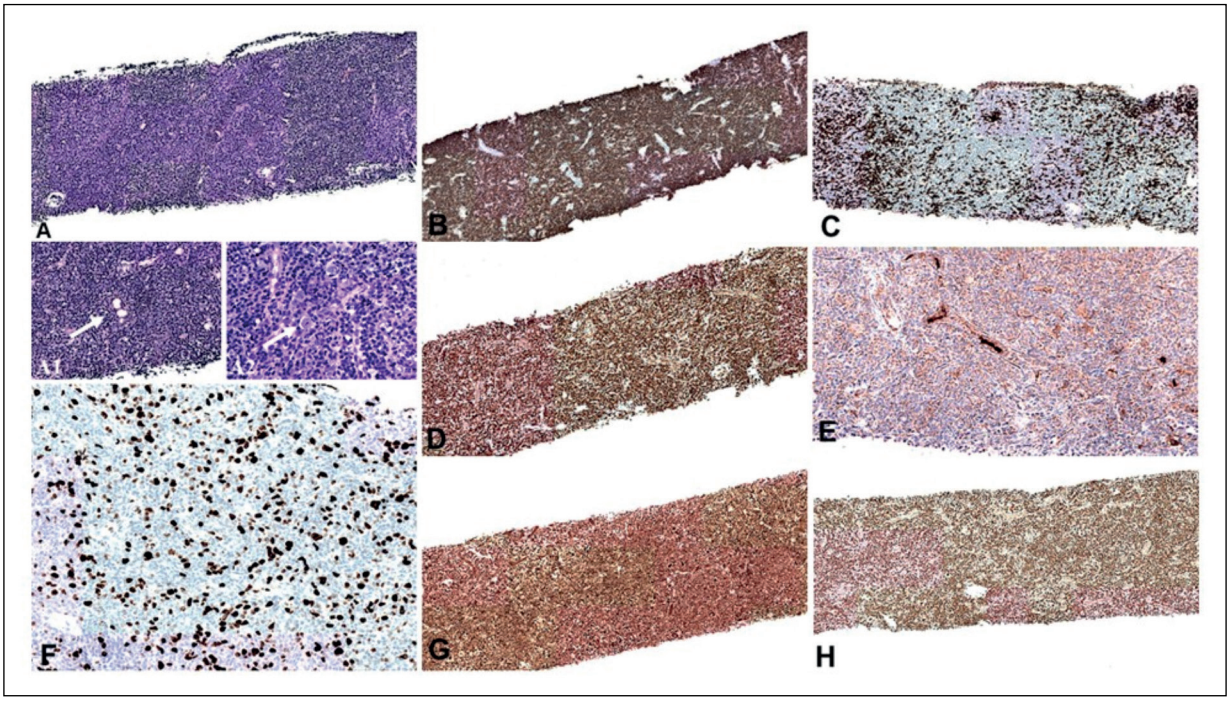

Figure 2. (Panels a-h). Histopathological and immunohistochemical features at liver biopsy: **Panel a.** Core needle biopsy showing a small-medium lymphoid cells proliferation, with the aspect of indented centrocytes, arranged in a diffuse growth pattern. In the insets A1 and A2, a residual ductal structure and a large Hodgkin-like cell (white arrows) Hematoxylin-Eosin staining). **Panel b.** Diffuse and strong staining for CD20. **Panel c.** Numerous and sparse small T-lymphocytes expressing CD3. **Panel d.** Diffuse and strong staining for BCL2, largely corresponding to CD20. **Panel e.** Negative staining for CD10 in the lymphoid population (positive internal control: luminal aspect of normal bile ducts). **Panel f.** Ki-67 proliferation index (about 20%). **Panel g.** Diffuse expression of BCL6. **Panel h.** Strong and diffuse staining for LMO2 (original magnification: panels a, b, c, d, g, h) 40×, panels a1, e) 100×, panels a2, f) 200×).

Discussion

In the present report, we describe a rare case of FHL, unexpectedly occurring in an old CD patient with no specific signs or symptoms related to the lymphoproliferative disorder. FNH represents the second most common benign liver tumor[5]. This diagnosis was, therefore, initially suspected, being then excluded according to demographic features, clinical characteristics and multidisciplinary MRI revision. A diagnosis of HA was subsequently presumed, due to the several concomitant risk factors in an old steroid-dependent CD patient (i.e. immunosuppression, age, sphincterotomy, recurrent ascending cholangitis)[5]. A progressive enlargement of the FHL despite antibiotics led to perform a potentially harmful, and therefore initially avoided, liver biopsy in the old steroid-dependent patient. Histological and immunophenotypic analysis lead to a diagnosis of hepatic FL. Reasons for the delayed diagnosis include the rarity of PHL and the observed unusual radiological images.

FL is the second most frequent subtype of nodal lymphoid malignancy in Western Europe (22% of all NHL)[2]. Secondary liver involvement in patients with B-cell lymphomas is relatively common (21%). Differently, PHL is very rare, representing only the 0.4% of all the reported primary extranodal NHL[3]. Follicular PHL is even rarer, representing only 1% to 4% of PHLs[4]. PHL is a liver-confined lymphoma, without extrahepatic involvement, often mimicking benign conditions[2-4]. Imaging visualize solitary or multiple hepatic nodules[3].

By our knowledge, only 9 cases of follicular PHLs have been described until 2019[6]. Typically, follicular PHL occurs in old males[4]. Clinical presentation may include abdominal pain without typical lymphoma-related symptoms. Blood chemistry may detect high levels of LDH (not observed in this case), with normal α-fetoprotein and CEA levels. The etiology and pathogenesis of PHL is undefined[4] and liver biopsy is required for a proper diagnosis[3]. Histology shows small to medium-sized centrocytes, giving rise to either

distinct follicles or diffuse areas with germinal center differentiation (CD10+, BCL6+, HGAL+, GCET2+, LMO2+), coexpressing BCL2[7]. The hallmark for diagnosing FL includes CD10+ cells in the interfollicular areas. The lack of expression of CD10 is more frequently observed in high-grade FL[7]. Even low-grade FL may show diminished staining in core needle biopsies, as interfollicular areas can be sampled instead of follicles, leading to weak or absent CD10 expression[3]. In these cases, additional germinal center markers are available in order to identify neoplastic cells (i.e. HGAL/GCET2, LMO2)[8]. In the reported case, the germinal center origin of neoplastic cells was confirmed by a strong and diffuse BCL6 and LMO2 positivity, despite CD10 negativity. Few morphological variants of FL have been described. Among the less common, FL with Hodgkin and Reed-Sternberg-like cells rises a differential diagnosis with HL[9]. In this patient, the absence of a polymorphic inflammatory background, together with only rare small T-cells (CD3+, CD57+, PD1+), not arranged in rosettes around the Hodgkin-like cells, helped to exclude a diagnosis of HL[3].

The diagnostic work-up of PHL includes a total body CT-scan and bone marrow examination[2]. Therapeutic options include watchful waiting, radiotherapy, chemoimmunotherapy or Rituximab, with concomitant methylprednisolone[2]. Risk factors for a poor prognosis include older age, systemic involvement, elevated serum liver enzymes, comorbidities. Survival is variable (from 3 to 123months, survival rate at 5-years: from 77% to 83% using chemotherapy)[10].

Conclusions

In the reported case, hepatic lymphoma occurred in a patient without CD-related risk factors (i.e. EBV infection, thiopurines use)[5-7]. However, general risk factors for lymphoma were present (i.e. long CD-history, old age, male gender and steroid-dependency potentially leading to immunosuppression). Whether the hepatic lesion was related to a secondary hepatic FL or to a PHL cannot be ascertained. The long-term steroids use may have masked lymph nodes involvement by FL. Initially, CT scan was incomplete (neck and pelvis not visualized) and no bone marrow examination was performed due to the old age. However, the histological and immunophenotypic characteristics of the progressively enlarged FHL, together with the absence of lymph node enlargements at baseline CT-scan, suggests a diagnosis of PHL.

We do believe that this report may focus the attention on the possible development of FL of the liver in CD. By our knowledge, follicular hepatic lymphoma as a primary or secondary involvement has not been described in CD.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Statement Authorship

LS: Wrote the manuscript with the contributions from BN, MC, RA, AM, GM; LB: Concept and design of the case report, critical revision of the manuscript and clinical assessments; CP, MM: Clinical assessment during hospitalization; MC, DN, IP: Hematological assessments; RA: US-guided liver biopsy and revision of all the radiological images; EC: Abdominal US; AM, MDP: Histopathological and immunohistochemical analysis of the liver biopsy. All authors read and approved the final manuscript.

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