CASE REPORT

Reactive lymphoid hyperplasia of the liver in a patient with multiple carcinomas: a case report and brief review

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A rare case of reactive lymphoid hyperplasia (RLH) of the liver in a 75-year-old woman admitted to hospital for surgical treatment of gastric, caecal and colon carcinomas is described here. Two nodular lesions in the left and right lobes of the liver were clinically diagnosed as metastatic tumours by computed tomography of the abdomen. A demarcating grey–white mass of size 1.4 cm was observed in a partially resected liver specimen. On examining the lesion microscopically, it was found to be composed of hyperplastic lymphoid follicles, lymphocytes, plasma cells, other inflammatory cells and interlaced hyalinised fibrous tissues. In the portal tracts around the lesion, chronic inflammatory cell infiltrates were seen, but no interface hepatitis or lymphoid follicle was observed. No evidence of monoclonality was observed by immunohistochemistry for B and T cell markers, in situ hybridisation for κ and λ light chains, and polymerase chain reaction analysis of immunoglobulin heavy chains or T cell receptor β and γ gene rearrangements. Bcl-2 immunoreactivity was not observed in the germinal centre. Epstein–Barr virus (EBV) antigen (latent membrane protein-1) and EBV-encoded small RNAs were not detected. A proliferation neither of myofibroblasts nor of cells positive for follicular dendritic cell markers was observed. RLH, formerly known as pseudolymphoma, has been reported of the liver in only 14 cases and is considered to be a differential diagnosis of small nodular lesions of the liver. That RLH has an inflammatory reactive nature, not a neoplastic disposition, and that EBV does not participate in the pathogenesis of RLH is supported by this case.

Pseudolymphoma was first defined in the lung by Saltzstein as a lymphocytic tumour associated with inflammation and with no evidence of systemic dissemination.¹ Subsequently, these apparently benign tumours were shown to be clonal proliferative lesions that could possibly develop into lymphoma. The term reactive lymphoid hyperplasia (RLH) is used for true benign lymphocytic tumour-like lesions with polyclonal features. RLH has been reported in various organs, but there have been only 14 cases reported of RLH of the liver.^{2–13} Here, we report an additional case of RLH of the liver and review the literature.

CASE REPORT

A 75-year-old woman was admitted to hospital for surgical treatment of gastric, caecal and colon carcinomas. She had no fever. We observed no evidence of a predisposing factor for steatohepatitis, such as obesity, diabetes mellitus and hyperlipidaemia, and the patient had no history of intake of drugs that caused hepatitis. Laboratory data showed no leucocytosis and negative results for hepatitis B virus surface antigen, anti-hepatitis C virus antibodies, antinuclear

antibodies and antimitochondrial antibodies. Immunoglobulin levels were within the normal range. On computed tomography of the abdomen, two similar nodular lesions in the left and right lobes of the liver were observed. Both tumours were preoperatively diagnosed to be metastatic. Distal gastrectomy, right hemicolectomy, sigmoidectomy and partial resection of the liver were performed. On computed tomography 6 months after the surgery, other metastatic lesions were observed in the liver and lungs.

PATHOLOGY

Macroscopic observation of the surgically resected liver specimens showed a well-circumscribed grey–white tumour measuring 1.4 cm in diameter in the left lobe (fig 1A). The second tumour measured 2.0 cm in size and was situated in the right lobe. When viewed microscopically, the lesion in the left lobe was an RLH lesion composed of hyperplastic lymphoid follicles preserving the mantle zone (fig 1B), with lymphocytes, plasma cells, other inflammatory cells and interlaced hyalinised fibrous tissue in the interfollicular area (fig 1C). No portal tract or bile duct was found in the lesion. In portal tracts around the lesion, chronic inflammatory cell infiltrates were seen, but no interface hepatitis or lymphoid follicles were observed (fig 1D). No evidence of an RLH lesion was observed in the other surgically resected specimens. The tumour in the right lobe was a moderately differentiated adenocarcinoma, and was considered to be a metastatic tumour originating from sigmoid colon carcinoma.

Immunohistochemical examination showed CD3-positive cells distributed mostly in the interfollicular area and CD79 α -positive cells mainly in the lymphoid follicles. This is similar to ordinary lymph nodes. Bcl-2 immunostaining was absent in the germinal centre (fig 1E), whereas CD23 was positive only in lymphoid follicles. No immunoreactivity for CD21 or Epstein–Barr virus (EBV) antigen (latent membrane protein-1) was observed. In in situ hybridisation studies, plasma cells positive for κ or λ light chain showed a polyclonal pattern in the interfollicular area (fig 1F,G). EBV-encoded small RNAs were not detected.

Molecular studies were carried out on DNA extracted from formalin-fixed, paraffin-wax-embedded tissue. With analysis by polymerase chain reaction (PCR), no evidence of monoclonal rearrangements of immunoglobulin heavy chains or T cell receptor β and γ genes was observed. The EBV genome was not detected with the polymerase chain reaction.

DISCUSSION

RLH is usually a small benign tumorous lesion, rarely observed in the liver. In all, 14 cases have been reported where RLH occurred in the liver (table 1). The female predominance is characteristic. Clinically, the tumours are

Abbreviations: EBV, Epstein–Barr virus; FDC, follicular dendritic cell; IPT, inflammatory pseudotumour; MALT, mucosa-associated lymphoid tissue; RLH, reactive lymphoid hyperplasia

Figure 1 (A) Cut surfaces of the surgical specimen of the liver showing a demarcating grey–white mass measuring 1.4 cm. (B) Hyperplastic lymphoid follicles appear diffusely in the lesion. (C) The lesion is composed of lymphoid follicles, lymphocytes, plasma cells, other inflammatory cells and interlaced hyalinised tissues, $\times 100$. (D) Portal tracts with chronic inflammatory cell infiltration are observed around the lesion, $\times 100$. (E) Bcl-2 immunoreactivity is absent in the germinal centre, $\times 100$. (F, G) In situ hybridisation for (F) κ light chain and (G) λ light chain, showing a polyclonal pattern, $\times 100$.

often misdiagnosed as hepatocellular carcinoma or metastatic tumour. Furthermore, it is difficult to make an accurate diagnosis through needle biopsy, and malignancy cannot be fully excluded in many cases. The final diagnosis is usually given from partially resected specimens.

The important differential diagnosis is mucosa-associated lymphoid tissue (MALT) lymphoma, inflammatory pseudotumour (IPT) or follicular dendritic cell (FDC) tumour. Morphological study showed lymphoproliferative appearances in multiple portal areas coalescing in MALT lymphoma. On the contrary, no portal tract or hepatocyte is usually present in RLH lesions composed of lymphoid follicles and various inflammatory cells. The lesion may occur in a portal tract and grow expansively, rather than developing simultaneously in plural portal tracts, fused to one lesion, such as MALT lymphoma. Although rearrangement of immunoglobulin heavy chain genes is often seen in MALT lymphoma, it was not detected in this case. IPTs represent infection-associated and reactive processes in most cases, but could also represent neoplastic lesions such as inflammatory myofibroblastic tumours.¹⁴ No characteristic clinical and

pathological features of IPTs, such as fever, myofibroblastic proliferation, xanthogranulomatous change and occlusive portal phlebitis, were observed in this case. A proliferation of FDCs was also not seen in this lesion. Recently, cases of IPT-like FDC tumours, a variant of FDC tumours, associated consistently with EBV infection were reported.¹⁵ There has been no reference to the association between RLH and EBV in the literature. In this case, there was no evidence that EBV was associated with the incidence of RLH by immunohistochemical, in situ hybridisation or molecular studies.

The pathogenesis of RLH in the liver has not yet been elucidated. Patients with this lesion had mostly presented with autoimmune disease, chronic hepatitis or carcinomas. One case was reported, where RLH developed after interferon α treatment for chronic hepatitis B.⁶ These results support the inflammatory reactive nature of this lesion. Our patient had triplicate carcinomas with liver metastasis. We thought that there was no direct relationship between an RLH lesion and multiple epithelial tumours, but immunoreaction against carcinoma cells may be associated with the development of this lesion.

Table 1 Clinicopathological features of reactive lymphoid hyperplasia of the liver

Case no.	Author	Age, sex	Background	Clinical diagnosis	Location of tumour	Size of tumour (cm)	Portal tract	Interfollicular fibrosis	Treatment	Comments
1	Snover <i>et al</i> ²	15, F	CID, PGF	ML	ND	ND	ND	ND	—	
2	Grouls ³	85, F	GC	ND	R	1.4; 0.8	—	+	—	Autopsy
3	Isobe <i>et al</i> ⁴	59, F	DM	MT	L	0.9	+	ND	PR	
4	Katayanagi <i>et al</i> ⁵	66, F	DM, CH	HCC	R	1.0	—	ND	PR	
5	Ohtsu <i>et al</i> ⁶	42, F	CHB	HCC	R	1.5	—	ND	PR	IFN α
6	Tanizawa <i>et al</i> ⁷	67, F	—	HCC	L	2	—	+	PR	
7	Kim <i>et al</i> ⁸	72, F	CHC, GC	HCC	L	1.7	+	ND	PR	
8	Nonomura <i>et al</i> ⁹	59, F	Hypertension	HCC	R	1.5	ND	ND	PR	
9	Nagano <i>et al</i> ¹⁰	47, F	Chronic thyroiditis	HCC	R	1.7	ND	ND	PR	
10	Sharifi <i>et al</i> ¹¹	52, F	PBC	—	R	0.4	—	+	—	Transplantation
11	Sharifi <i>et al</i> ¹¹	56, F	PBC, CREST	—	L	1.5	ND	ND	—	Transplantation
12	Sharifi <i>et al</i> ¹¹	56, M	DIH	—	ND	0.7	—	ND	PR	
13	Okubo <i>et al</i> ¹²	49, F	Sjögren syndrome	HCC	R	2.0	ND	ND	PR	
14	Pantanowitz <i>et al</i> ¹³	69, F	RCC	Metastasis	R	1.7	—	+	PR	
15	Sato <i>et al</i> (present case)	75, F	GC, CoC, CeC	Metastasis	L	1.4	—	+	PR	

CeC, caecal carcinoma; CH, chronic hepatitis; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CID, combined immunodeficiency; CoC, colon carcinoma; CREST, calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia; DIH, drug-induced hepatitis; DM, diabetes mellitus; F, female; GC, gastric carcinoma; HCC, hepatocellular carcinoma; IFN, interferon; L, left lobe; M, male; ML, malignant lymphoma; MT, malignant tumour; ND, not determined; PBC, primary biliary cirrhosis; PGF, polyglandular failure syndrome; PR, partial resection; R, right lobe; RCC, renal cell carcinoma.

Take-home messages

- Reactive lymphoid hyperplasia (RLH) of the liver is a rare benign lesion presenting as a small nodule.
- Histologically, this lesion consists of hyperplastic lymphoid follicles, lymphocytes, plasma cells and other inflammatory cells.
- No evidence was found that the Epstein-Barr virus contributed to the development of the lesion.
- RLH has an inflammatory reactive nature, not a neoplastic disposition.
- To the best of our knowledge, this is the first report of RLH associated with multiple carcinomas.

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