Primary Hepatic Lymphoma Complicated by a Hepatic Inflammatory Pseudotumor and Tumor-Forming Pancreatitis

Rena Kaneko1, Hiroyuki Mitomi2, Natsuko Nakazaki1, Yuichiro Yano1, Masazumi Ogawa1, Yuzuru Sato1

1) Department of Gastroenterology, and 2) Department of Diagnostic Pathology, Japan Organization of Occupational Health and Safety Kanto Rosai Hospital, Kawasaki City, Kanagawa, Japan

Address for correspondence:
Rena Kaneko
211-8510 Kizukisumiyoshi 1-1, Nakahara, Kawasaki City, Kanagawa, Japan
renakantoh.johas.go.jp

Received: 21.05.2017
Accepted: 02.06.2017

ABSTRACT

Background: Hepatic inflammatory pseudotumor (IPT) is considered to be benign in biological behavior, and its malignant transformation is extremely rare. There has only been one published case of primary hepatic lymphoma complicated by hepatic IPT.

Case presentation: A 73-year-old man presented with obstructive jaundice and a pancreatic head mass. Histology of the mass revealed chronic pancreatitis with lymphoid follicle formation, leading to a diagnosis of a suspicion of follicular pancreatitis. After a choledochojejunostomy, a hepatic tumor was detected, and a biopsy revealed lymphoplasmacytic infiltration. Immunohistochemistry confirmed the polyclonal nature of lymphoplasma cells, indicative of an IPT. The hepatic tumor disappeared during follow-up, but the patient exhibited a high fever related to tumor recurrence. A biopsy revealed the co-existence of a diffuse large B-cell lymphoma and an IPT. IgG4-related disease was excluded because storiform fibrosis, obliterative phlebitis, and a significant increase in IgG4-immunoreactive cells were absent in all investigated tissues. The tumor completely disappeared after chemotherapy.

Conclusion: Careful observation is necessary in this kind of situation because the presence of a hepatic IPT may represent an increased risk of malignant transformation.

Key words: inflammatory pseudotumor – malignant transformation – diffuse large B-cell lymphoma – primary hepatic lymphoma – follicular pancreatitis.

Abbreviations: IPT: inflammatory pseudotumor; DLBCL: diffuse large B-cell lymphoma; CT: computed tomography; LDH: lactate dehydrogenase; sIL-2R: soluble interleukin-2 receptor; EBER: Epstein-Barr virus-encoded small RNA; R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone

INTRODUCTION

A hepatic inflammatory pseudotumor (IPT) is histologically characterized by proliferating fibrous tissue and inflammatory cells, and is generally considered to be benign in its biological behavior [1-6]. However, it can clinically masquerade as a malignant growth such as a hepatocellular carcinoma or a metastatic tumor [2-4]. In some cases, an aggressive course of hepatic IPT has been reported [2, 5]. The malignant transformation of hepatic IPT is extremely rare [7, 8] and, to our knowledge, there has only been one case published of primary hepatic lymphoma arising from a hepatic IPT [7].

Tumor-forming pancreatitis has been called an inflammatory pancreatic mass [9] or pseudotumoral pancreatitis [10], and mostly involves the pancreas head with obstructive jaundice [9]. Most recently, a variant of tumor-forming pancreatitis named follicular pancreatitis has been described [11-13], histologically differing from autoimmune pancreatitis [11].

Here, we report a rare case of a hepatic diffuse large B-cell lymphoma (DLBCL) complicated with a hepatic IPT in a patient with tumor-forming, lymphoplasmacytic pancreaticitis.

CASE PRESENTATION

A 73-year-old Japanese man was referred to our hospital because of obstructive jaundice. He had undergone a cholecystectomy at 62 years of age. A solitary low-density mass was present in the pancreas head as revealed by computed
tomography (CT) (Fig. 1). These imaging observations led to a diagnosis of a pancreas head cancer. A choledochojunostomy was performed because intraoperative frozen sections showed atrophic parenchyma, fibrosis, and lymphoid follicle formation, but no malignant cells. During surgery, biopsy samples were excised from the thickened common bile duct and periporal lymph nodes. Subepithelial fibrosis and an infiltration of lymphoplasma cells were detected in the bile duct wall, and lymph follicle hyperplasia with an increase in plasma cells was observed in the lymph nodes.

After a choledochojunostomy, the pancreas head mass gradually decreased in size and finally disappeared. The patient suffered an intermittent high fever which was successfully treated with antibiotics. At 46 months after surgery, a circular, low-density tumor was found in the left hepatic lobe (Fig. 2A). The tumor gradually shrank, and finally formed a scar without therapy (Fig. 2B). Recurrence occurred as a hypovascular tumor in the right lobe 76 months after surgery, but also disappeared without therapy. Subsequently, a well-demarcated tumor was observed along the intrahepatic bile ducts of the right anterior segment 81 months after surgery (Fig. 2C). At this time, soluble interleukin-2 receptor (sIL-2R) was 523 U/ml. A liver biopsy was performed for the first time, which demonstrated a severe lymphoplasma cell infiltration (Fig. 3). CD20-positive B-cells and CD3-positive T-cells were detected by immunohistochemistry, supporting a diagnosis of hepatic IPT. Ninety-five months after surgery, the patient had an intermittent high fever, and the hepatic tumor had expanded. Histologically, a second biopsy of the tumor also revealed an IPT. Flow cytometry of the tumor following CD45 gating for lymphocytes detected 80% CD3/CD5/CD7-positive cells (T-cell lineage) and 20% CD19/CD20-positive cells (B-cell lineage), with the B-cell population showing almost equal expression of kappa and lambda immunoglobulin light chains. Subsequently, an excisional biopsy of the mesenteric lymph node was performed, and the histology was considered to be benign (sIL-2R, 928 U/l).

The patient had a persistently high fever, and the hepatic tumor had increased to 10 cm in size 102 months after surgery (Fig. 4). On abdominal ultrasound examination, two biopsy specimens (3rd) were taken from different regions of the hepatic tumor. One specimen obtained from the boundary of the tumor showed an IPT (Fig. 5A) with CD20-positive B-cells and CD3-positive T-cells (Figs. 5B, C). The other specimen obtained from the interior of the tumor had a diffuse proliferation of large atypical cells (Figs. 6A, B) composed solely of CD20-positive and CD3-negative B-cells, indicating a DLBCL (Figs. 6C, D). In consideration of these findings, the hepatic tumor was finally diagnosed as a DLBCL complicated with an IPT. The tumor decreased in size and disappeared after six cycles of treatment with the monoclonal antibody rituximab plus a cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) regimen. During the 12-month follow-up after R-CHOP therapy, no recurrence was observed and the patient’s condition was good at the most recent visit.

Immunohistochemical analysis of CD138, IgG, and IgG4 was performed. Results from histological analysis, immunohistochemistry, and in situ hybridization for Epstein-Barr virus-encoded small RNA (EBER)-1 are summarized in Table I. IgG4-positive cells were increased in the bile duct and periportal lymph node, but not in the other tissues.
Fig. 3. Histology of the first hepatic tumor biopsy. Severe lymphoplasma cell infiltration (H&E ×100).

Fig. 4. CT image 102 months after surgery. The recurrent hepatic tumor measured 10 cm in size.

Fig. 5. Histology of the boundary of the hepatic tumor. A: Severe lymphoplasmacytic infiltrate (H&E ×100). B, C: Aggregated lymphocytes demonstrating positive staining for CD20 (B) and CD3 (C) (immunoperoxidase ×100).

DISCUSSION

In this case, tumor-forming pancreatitis was initially observed, with its subsequent development into a recurrent hepatic IPT, followed by a hepatic DLBCL.

On CT imaging, a hepatic IPT appeared as a low-density mass [4-6]. The area of low attenuation in this lesion reflects the presence of chronic inflammatory changes, including histiocytes and lymphoplasamyctes, while areas of iso- or high attenuation represent fibroblastic proliferation [5]. In our case, the hepatic IPT was initially circular with low attenuation, consistent with the major histological features of lymphoplasmacytic proliferation. We subsequently observed a spontaneous regression of the hepatic IPT, similar to several reported cases [3, 6]. Lopez et al. hypothesized that a hepatic IPT is an exuberant hepatic reaction to bile stasis because the reestablishment of bile flow seems to be a definitive event in its regression. Although the etiology of an IPT remains unclear, an important mechanism is that it can develop as a complication of cholangitis [2-6]. In the present case, the recurrent IPT appeared as an unusual tumor formation along the intrahepatic bile ducts, probably due to the development of intrahepatic cholangitis with biliary stasis or regurgitation after a choledochojejunostomy.

There has only been one other published case of a primary hepatic lymphoma arising from a hepatic IPT [7]. In that report, the hepatic tumor remained stable for 4 years, after which a sudden enlargement of the mass signalled its malignant transformation. The first biopsy showed that the hepatic mass was diagnosed as an IPT. However, the final resected hepatic mass was composed of a DLBCL. Similar to our case, it appeared that a hepatic DLBCL arose from a hepatic IPT, suggesting that chronic inflammatory stimulation of B-cells may lead to a polyclonal origin and, later, the monoclonal expansion of these cells.

Primary hepatic lymphoma is a rare condition, making up less than 1% of all extranodal lymphomas [14, 15]. On CT imaging of a primary hepatic lymphoma, homogeneous low-attenuation masses are often detected [14] and misdiagnosed as hepatic inflammatory disease, including IPT. Our case fulfilled the definition of a primary hepatic lymphoma, that is, confined to the liver, and not found in the spleen, lymph nodes or bone marrow [16]. Surgical resection, chemotherapy, and radiotherapy are currently available as treatment modalities for primary hepatic lymphoma, but treatment is complicated by the rarity and heterogeneity of the disease [14, 15]. Chemotherapy is the recommended treatment option for extranodal DLBCL, and a R-CHOP regimen has recently become the standard therapy[17]. Our patient responded to R-CHOP chemotherapy, similar to a previous case of a primary hepatic lymphoma that was
<table>
<thead>
<tr>
<th>Specimen</th>
<th>Pancreas</th>
<th>Bile duct</th>
<th>Lymph node (periportal region)</th>
<th>Liver</th>
<th>Liver</th>
<th>Liver (Boundary of the tumor)</th>
<th>Liver (Inside of the tumor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after surgery *</td>
<td>0 (At surgery)</td>
<td>0 (At surgery)</td>
<td>0 (At surgery)</td>
<td>81 months</td>
<td>93 month</td>
<td>102 months</td>
<td>102 months</td>
</tr>
<tr>
<td>Histology</td>
<td>Chronic lymphoplasmacytic pancreatitis</td>
<td>Chronic choledochitis</td>
<td>Lymph follicle hyperplasia</td>
<td>Inflammatory pseudotumor</td>
<td>Inflammatory pseudotumor</td>
<td>Inflammatory pseudotumor</td>
<td>Malignant lymphoma</td>
</tr>
<tr>
<td>- Lymphoplasmacytic infiltrate</td>
<td>- Lymphoplasmacytic infiltrate</td>
<td>- Enlarged follicular center</td>
<td>- Lymphocytic infiltrate without eosinophilic infiltrate</td>
<td>- Lymphocytic infiltrate without eosinophilic infiltrate</td>
<td>- Lymphocytic infiltrate</td>
<td>- Lymphocytic infiltrate</td>
<td>- Diffuse infiltration of enlarged lymphoma cells</td>
</tr>
<tr>
<td>- Lymphoid follicle formation</td>
<td>- Lymphoid follicle formation</td>
<td>- Plasmacytic infiltrate in interfollicular area</td>
<td>- Interface hepatitis-like lesion</td>
<td>- Interface hepatitis-like lesion</td>
<td>- Interface hepatitis-like lesion</td>
<td>- Interface hepatitis-like lesion</td>
<td>- Destruction of hepatic parenchyma</td>
</tr>
<tr>
<td>- Atrophic acinar cells and fibrosis</td>
<td>- Fibrosis and glandular proliferation</td>
<td>- Absence of atypical lymphocytes</td>
<td>- Degeneration of interlobular bile ducts</td>
<td>- Degeneration of interlobular bile ducts</td>
<td>- Periportal fibrosis</td>
<td>- Absence of lymphoepithelial lesions</td>
<td></td>
</tr>
<tr>
<td>- Absence of neutrophilic or eosinophilic infiltrate</td>
<td>- Absence of neutrophilic or eosinophilic infiltrate</td>
<td>- Absence of abscess or necrosis</td>
<td>- Absence of abscess or necrosis</td>
<td>- Absence of abscess or necrosis</td>
<td>- Absence of abscess or necrosis</td>
<td>- Absence of abscess or necrosis</td>
<td></td>
</tr>
<tr>
<td>- Absence of striform fibrosis or obliterator phlebitis</td>
<td>- Absence of striform fibrosis or obliterator phlebitis</td>
<td>- Absence of striform fibrosis or obliterator phlebitis</td>
<td>- Absence of striform fibrosis or obliterator phlebitis</td>
<td>- Absence of striform fibrosis or obliterator phlebitis</td>
<td>- Absence of striform fibrosis or obliterator phlebitis</td>
<td>- Absence of striform fibrosis or obliterator phlebitis</td>
<td></td>
</tr>
<tr>
<td>Immunohistochemistry and in situ hybridization</td>
<td>CD3+ T-cells and CD20+ B-cells distributed in the lymphoid follicle</td>
<td>CD3+ T-cells and CD20+ B-cells distributed in the bile duct wall</td>
<td>CD3+ T-cells and CD20+ B-cells distributed in the bile duct wall</td>
<td>CD3+ T-cells and CD20+ B-cells distributed in liver tissue</td>
<td>CD3+ T-cells and CD20+ B-cells distributed in liver tissue</td>
<td>CD3+ T-cells and CD20+ B-cells distributed in liver tissue</td>
<td>Positive for CD20 and negative for CD3 in lymphoma cells</td>
</tr>
<tr>
<td>CD138+ plasma cells distributed in the atrophic pancreatic tissue</td>
<td>CD138+ plasma cells distributed in the bile duct wall</td>
<td>CD138+ plasma cells distributed in the bile duct wall</td>
<td>CD138+ plasma cells distributed in follicular center area</td>
<td>CD138+ plasma cells distributed in follicular center area</td>
<td>CD138+ plasma cells distributed in follicular center area</td>
<td>CD138+ plasma cells distributed in follicular center area</td>
<td>Negative for CD15, cyclin D1 and CD56 in lymphoma cells</td>
</tr>
<tr>
<td>CD138+ plasma cells predominantly distributed in interfollicular area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative for CD10, cyclin D1 and CD56 in lymphoma cells</td>
</tr>
<tr>
<td>Positive for EBER-1 in situ hybridization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative for EBER-1 in situ hybridization</td>
</tr>
<tr>
<td>Negative for ALK immunostaining</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative for ALK immunostaining</td>
</tr>
<tr>
<td>Negative for EBER-1 in situ hybridization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative for ALK immunostaining</td>
</tr>
<tr>
<td>Negative for ALK immunostaining</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative for ALK immunostaining</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunoreactive indices</th>
<th>CD138 immunoreactive cells*</th>
<th>IgG immunoreactive cells*</th>
<th>IgG4 immunoreactive cells*</th>
<th>IgG4 / IgG immunoreactive cells (%)</th>
<th>IgG4 / CD138 immunoreactive cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD138 immunoreactive cells**</td>
<td>51 / HPF</td>
<td>204 / HPF</td>
<td>1 / HPF</td>
<td>NE</td>
<td>35 / HPF</td>
</tr>
<tr>
<td>IgG immunoreactive cells*</td>
<td>28 / HPF</td>
<td>180 / HPF</td>
<td>1 / HPF</td>
<td>NE</td>
<td>1 / HPF</td>
</tr>
<tr>
<td>IgG4 immunoreactive cells*</td>
<td>20 / HPF</td>
<td>148 / HPF</td>
<td>1 / HPF</td>
<td>NE</td>
<td>1 / HPF</td>
</tr>
<tr>
<td>IgG4 / IgG immunoreactive cells (%)</td>
<td>71</td>
<td>82</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>IgG4 / CD138 immunoreactive cells (%)</td>
<td>NE</td>
<td>31</td>
<td>73</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

* Choledochojunostomy; ** Mean values of three high power fields (HPF, X400); NE, not evaluated; ALK, anaplastic lymphoma kinase; EBER-1, Epstein-Barr virus-encoded small RNA-1
also sensitive to a R–CHOP regimen [18]. When an accurate diagnosis of a hepatic IPT is made by liver biopsy, conservative therapy is better, since few hepatic IPTs are considered to be potentially premalignant and leading to a life-threatening illness [7, 8].

Follicular pancreatitis histologically resembles autoimmune pancreatitis with prominent lymphoid follicles, but lacks storiform fibrosis, obliterator phlebitis, granulocytic epithelial lesions or prominent IgG4-positive plasma cells, and has existed as an under-recognized disease entity among the category of lymphoplasmacytic pancreatitis [11-13].

Similarly, pancreatic localized lymphoid hyperplasia or pseudolymphoma shows lymphoid follicles composed of germinal centers surrounded by rims of lymphocytes, and lymphoplasmacytic infiltration with an increased collagenous stroma [19, 20]. In addition, Zen et al. proposed a disease entity named follicular cholangitis and pancreatitis, which showed prominent duct-centered lymphoplasmacytic infiltration and lymphoid follicles with collagenous fibrosis in a pancreatobiliary lesion [11]. In our case, we observed chronic lymphoplasmacytic pancreatitis and cholangitis with lymphoid follicle formation, but not storiform fibrosis, granulocytic epithelial lesions, obliterator phlebitis or a marked increase of IgG4-positive plasma cells, thus resembling "follicular cholangitis and pancreatitis". However, prominent duct-centered lymphoplasmacytosis could not be detected because of the small size of pancreatic samples obtained at surgery. To the best of our knowledge, there is no report of the causal relationship between mass forming pancreatitis and liver IPT except for IgG4-related disease.

In our case, IgG4-positive cells were increased in the bile duct and periporal lymph nodes, but not in other tissue samples. Storiform fibrosis or obliterator phlebitis were not present in any tissues. Further, no elevation was found in the IgG4 serum level (68.9 mg/dL). Retroperitoneal fibrosis and other manifestations of IgG4-related disease were not detected in imaging procedures and careful clinical examinations. In consideration of these findings, we excluded IgG4-related disease.

CONCLUSION

We described here a case of a hepatic lymphoma complicated with a hepatic IPT and lymphoplasmacytic (follicular) pancreatitis. This case supports the hypothesis that an IPT can transform into a malignant lymphoma. Careful observation of such cases is necessary since the development of an IPT may include the risk of a transformation to malignancy. The early detection of transformations is vital for choosing suitable and effective therapies for such cases of hepatic lymphoma.

Conflicts of interest: No conflict of interest to declare.

Authors’ contribution: R.K. wrote the report. H.M. made the pathology examination. N.N., Y.Y., M.O. and Y.S. attended in the therapeutical management.

REFERENCES