



Spontaneous regression of hepatic inflammatory pseudotumor with primary biliary cirrhosis: Case report and literature review

Hiroshi Koide, Ken Sato, Toshio Fukusato, Kenji Kashiwabara, Noriaki Sunaga, Takafumi Tsuchiya, Saeko Morino, Naondo Sohara, Satoru Kakizaki, Hitoshi Takagi, Masatomo Mori

Hiroshi Koide, Ken Sato, Noriaki Sunaga, Takafumi Tsuchiya, Saeko Morino, Naondo Sohara, Satoru Kakizaki, Hitoshi Takagi, Masatomo Mori, Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Gunma 371-8511, Japan

Toshio Fukusato, Department of Pathology, Teikyo University School of Medicine, Itabashi-ku, Tokyo 173-8605, Japan

Kenji Kashiwabara, Clinical Pathology, Gunma University Graduate School of Medicine, Maebashi, Gunma 371-8511, Japan

Correspondence to: Ken Sato, MD, PhD, Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan. satoken@showa.gunma-u.ac.jp

Telephone: +81-27-2208127 Fax: +81-27-2208136

Received: 2005-06-07 Accepted: 2005-07-28

Abstract

Hepatic inflammatory pseudotumor (IPT) is a rare benign non-neoplastic lesion characterized by proliferating fibrous tissue infiltrated by inflammatory cells. The exact etiology of IPT remains unclear. Although the association of IPT with systemic inflammatory disorders has been well established, a specific relationship with cholangitis is distinctly rare. We report a case of spontaneous regression of hepatic IPT with primary biliary cirrhosis (PBC). To date, only two cases of IPT with PBC have been reported. In our case, however, IPT developed during the course of improvement of cholangitis of PBC induced by effective treatment, differing from two previously reported cases. Our case indicates that the development of IPT does not also relate to the activity of cholangitis and/or hyper gamma-globulinemia, since our case was confirmed radiologically to be free of IPT when biliary enzymes and immunoglobulins were much higher than the corresponding values on admission. Comparison of our case with the two previously reported cases suggests that IPT occurring with PBC does not represent the same disease entity or be a bystander for PBC.

© 2006 The WJG Press. All rights reserved.

Key words: Hepatic inflammatory pseudotumor; Primary biliary cirrhosis; Spontaneous regression; Ursodeoxycholic acid; Bezafibrate

Koide H, Sato K, Fukusato T, Kashiwabara K, Sunaga N, Tsuchiya T, Morino S, Sohara N, Kakizaki S, Takagi H,

Mori M. Spontaneous regression of hepatic inflammatory pseudotumor with primary biliary cirrhosis: Case report and literature review. *World J Gastroenterol* 2006; 12(10): 1645-1648

<http://www.wjgnet.com/1007-9327/12/1645.asp>

INTRODUCTION

Hepatic inflammatory pseudotumor (IPT) is a rare benign non-neoplastic lesion characterized histopathologically by proliferating fibrous tissue infiltrated by inflammatory cells. The exact etiology of IPT remains unclear. Although the association of IPT with systemic inflammatory disorders has been well described, a specific relationship with cholangitis is distinctly rare^[1-4]. Primary biliary cirrhosis (PBC) is a chronic cholestatic disease with cholangitis. We report a case of spontaneous regression of IPT associated with PBC. Our case was peculiar in view of detection of IPT during improvement of cholangitis of PBC, thus differing from the two previous reports of IPT with PBC^[5,6].

CASE REPORT

The patient was a 71-year-old man. He was diagnosed in 2001 with PBC (Scheuer's histological stage II) based on histopathological findings of liver biopsy specimens and positive anti-mitochondrial antibody (AMA) and was followed with ursodeoxycholic acid (UDCA) in our department. He requested a check up for cancer and fluorodeoxyglucose positron emission tomographic study (FDG PET) was performed on his request on his 70th birthday. The whole-body images demonstrated a 3-cm-diameter spherical mass in the liver (Figure 1A, B). One year before FDG PET, no liver tumor was noted on enhanced computerized tomography (CT). He was admitted to our department for full examination and assessment. We had started treating the patient with bezafibrate, which was recently reported to be effective in improving PBC patients with elevated biliary enzymes^[7], two months before detection of the liver mass because UDCA had not been fully effective. On admission, he was asymptomatic and physical examination was negative. Laboratory data on admission (Table 1) showed elevated

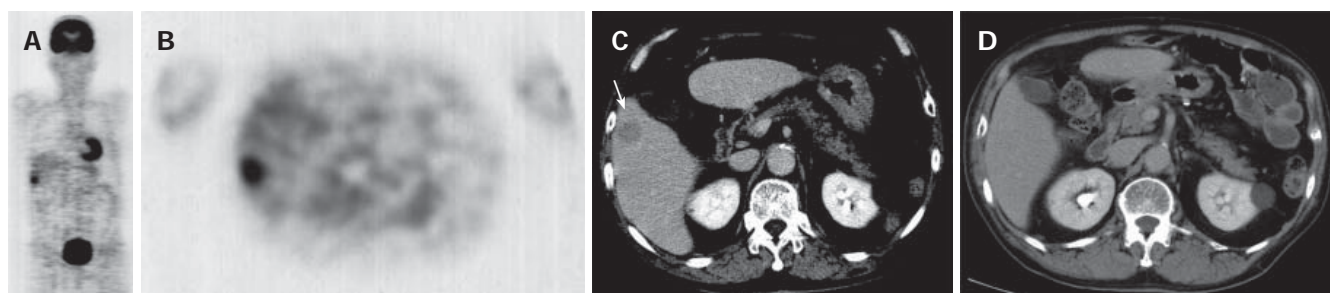


Figure 1 A, B: Whole body F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan showed a 3-cm spherical mass in the right lobe of the liver. A: Coronal sectional view, B: horizontal sectional view. C: Enhanced CT showed a 3-cm spherical low-density mass (arrow) in the right lobe of the liver. D: Another enhanced CT performed 3 mo after targeted liver biopsy showed complete resolution of the mass.

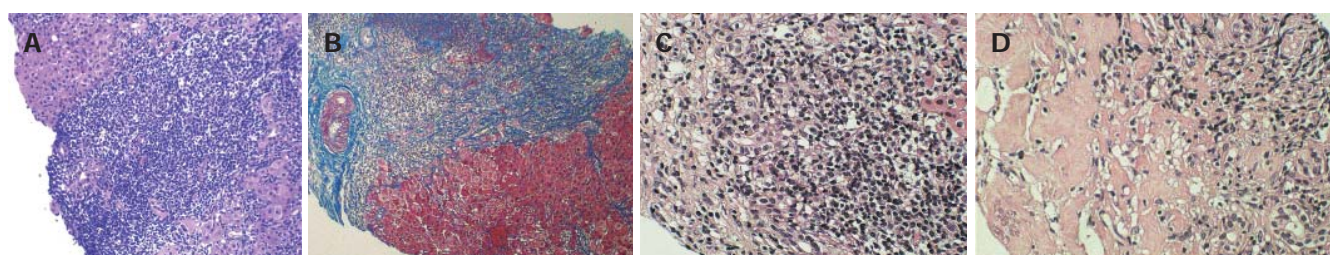


Figure 2 A: Liver biopsy specimen from the non-tumorous liver. Histopathological findings are consistent with primary biliary cirrhosis. The enlarged portal tract with damaged bile ducts in florid lesion of non-suppurative destructive cholangitis is infiltrated by inflammatory mononuclear cells. H&E, X100. B: Liver biopsy specimen shows clear-cut boundary between the "tumor" and liver parenchyma. Azan-Mallory, x100. C: The "tumor" is composed of chronic inflammatory cells including lymphocytes and plasma cells. H&E, x400. D: The "tumor" is composed of fibrous tissue, thick hyalinized collagen bundles with disappearance of liver parenchyma. H&E, x400.

Table 1 Changes of Biochemical and immunologic Profile

	Before treatment of UDCA without detection of IPT	On admission	At the time of regression of IPT
Total bilirubin (mg/dL)	0.7	0.8	0.6
AST (IU/L)	46	22	25
ALT (IU/L)	391	16	15
ALP (IU/L)	682	159	141
γGTP (IU/L)	248	52	45
IgM (mg/dL)	1010	303	281
IgG (mg/dL)	2010	1360	1170
ANA	×5120	×160	×160
AMA (index)	181	205.6	173.2
CRP	<0.1	<0.1	<0.1

AMA (205.6 arbitrary unit), anti-nuclear antibodies (ANA, ×160), gamma-glutamyl transpeptidase (gamma-GTP, 52 IU/L) and IgM (303 mg/dL) levels and a normal value of alkaline phosphatase (ALP). The results of these tests showed satisfactory improvement compared with the data recorded when treatment was limited to UDCA only, thus reflecting the effectiveness of bezafibrate. Total bilirubin, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, IgG levels, leukocyte count and gamma-globulin ratio of serum protein were normal. Serology for hepatitis B and C, alpha-fetoprotein, protein levels induced by the absence of vitamin K or antagonist-II and carcinoembryonic antigen were normal. Magnetic resonance cholangiopancreatography (MRCP) findings were normal. Enhanced CT showed a 3-cm spherical low-density mass in the right lobe of the liver (Figure

1C) corresponding to the mass on FDG PET. To rule out hepatocellular carcinoma, metastatic liver tumor, and cholangiocarcinoma, percutaneous needle biopsy was performed under CT because of the isoechoic lesion by ultrasonography. Histopathological examination showed marked infiltration of lymphocytes, plasma cells, fibrosis and loss of hepatic cells, findings consistent with IPT (Figure 2). Immunohistochemical staining for kappa- and lambda-light chains of immunoglobulin demonstrated the plasma cells contained both chains almost equally. The patient was followed up conservatively, and a repeat CT scan 3 mo after biopsy showed complete regression of IPT (Figure 1D). At this point, laboratory data (Table 1) showed normalization of gamma-GTP level and improvement of AMA (173.2 arbitrary unit) and IgM (281 mg/dL) levels except the same level of ANA (×160).

DISCUSSION

IPT is acute benign lesion that develops throughout the body. Hepatic IPT is relatively unique but has been recognized with increased frequency. It is difficult to make a specific diagnosis based on the findings of laboratory or imaging techniques because there is no specific laboratory marker and radiographic appearance. Therefore the vast majority of reported cases of IPT of the liver have been diagnosed after surgery or at autopsy^[8-11]. Recently ultrasonography-guided percutaneous liver biopsy is reported to be useful^[10,12].

The CT or MRI appearance of abdominal IPT are variable^[13]. Moreover it has been reported that there are no specific signs of the disorder, in spite of the advances in imaging techniques (ultrasonography, endoscopic

retrograde cholangiography and angiography)^[14-16], Yoon *et al.*^[17] reported that the area of low attenuation indicated the presence of chronic inflammatory infiltrations with foamy histiocytes, plasmacytes, and lymphocytes, while areas of iso- or high attenuation represents fibroblastic proliferation. Therefore the low attenuation of IPT on CT findings in our case may indicate a lower component of fibrosis and a higher component of cellular infiltration. Interestingly, to our knowledge, there is only one case of IPT detected by FDG PET, resulting from foreign body in abdominal cavity^[18]. The tumor mass was identified as an inflammatory granuloma^[18]. FDG PET may reflect inflammatory cell infiltrations in IPT in our case. The protean radiologic manifestations of IPT in our case may be the result not only of the variable morphologic structure including hyalinized collagen bundles or inflammatory cell infiltrations but the dynamic, rapidly changing nature of an inflammatory process.

While the exact etiology of hepatic IPT remains unclear, several mechanisms have been postulated such as infection, immune reaction, intraparenchymal hemorrhage and necrosis, occlusive phlebitis of intrahepatic veins, and secondary reaction to intrahepatic rupture of a biliary radical^[19]. Cholangitis arising from various causes including infection with microorganisms, immunological or allergic reactions, and primary sclerosing cholangitis (PSC) has been also considered responsible for the development of hepatic IPT^[1-4]. In only two recent reports^[5,6], PBC was proposed as a possible cause of hepatic IPT. In both of these cases, hepatic IPT was detected with the simultaneous discovery of PBC or untreated PBC, associated with extremely high levels of biliary enzymes and autoimmune antibodies. Hyper gamma-globulinemia has been also suggested to contribute to the development of IPT^[20-22]. The activity of cholangitis or hyper gamma-globulinemia as the etiological factor is, however, cannot be applied to our case because ANA (X5120), ALP (682 IU/L), gamma-GTP (248 IU/L), IgG (2010 mg/dL) and IgM levels (1010 mg/dL), measured when hepatic IPT had not been detected by CT before treatment of UDCA, were much higher than the corresponding laboratory data on admission (Table 1). At the time of regression of IPT, some of the laboratory data (Table 1) improved compared to those on admission probably due to effectiveness of UDCA add-on bezafibrate. However causal association between development or regression of IPT and improvement of laboratory data remains uncertain. Importantly, our case suggests IPT can develop at relatively inactive or recovery phase of PBC differing from previous reports^[5,6] and on the contrary, IPT with PBC is probably not the same disease entity or a bystander for PBC.

The other finding exemplifying disease diversity is that the rapid resolution of some cases^[4], including our case, may be related to the effectiveness of treatment of the underlying disease whereas in the other reported case^[5] IPT regressed even though UDCA did not effectively improve the laboratory data. With regard to treatment of IPT, most reported patients underwent surgical resection because it is difficult to distinguish IPT from malignant liver tumors using only imaging modalities^[9,23]. However, the prognosis of hepatic IPT is usually benign. Based on its spontaneous

regression property, it is suggested that treatment of IPT should be conservative or noninvasive in patients diagnosed by imaging or needle biopsy^[24]. As a treatment protocol, we recommend the use of medications first, such as UDCA and/or bezafibrate for patients with IPT and PBC or PSC after making a definite diagnosis. Once PBC is diagnosed, it is advised to follow such patients regularly and carefully by imaging studies to rule out the development of hepatic IPT during the clinical course, like our case. Since IPT rarely arises in PBC, but hepatocellular carcinoma often develops in cirrhotic patients with PBC, IPT may be one of hepatic tumors arising in PBC patients as a differential diagnosis during the clinical course. The coexistence of hepatic IPT and PBC, however, may be an accidental event. Further cases need to be diagnosed and studied in more detail.

REFERENCES

- 1 Gough J, Chakrabarti S. Inflammatory pseudotumor of the liver in a patient with chronic sclerosing cholangitis. *Am J Gastroenterol* 1993; **88**: 1452-1453
- 2 Nakanuma Y, Tsuneyama K, Masuda S, Tomioka T. Hepatic inflammatory pseudotumor associated with chronic cholangitis: report of three cases. *Hum Pathol* 1994; **25**: 86-91
- 3 Nonomura A, Minato H, Shimizu K, Kadoya M, Matsui O. Hepatic hilar inflammatory pseudotumor mimicking cholangiocarcinoma with cholangitis and phlebitis--a variant of primary sclerosing cholangitis? *Pathol Res Pract* 1997; **193**: 519-525; discussion 526
- 4 Toda K, Yasuda I, Nishigaki Y, Enya M, Yamada T, Nagura K, Sugihara J, Wakahara T, Tomita E, Moriwaki H. Inflammatory pseudotumor of the liver with primary sclerosing cholangitis. *J Gastroenterol* 2000; **35**: 304-309
- 5 Hosokawa A, Takahashi H, Akaike J, Okuda H, Murakami R, Kawahito Y, Tokuno T, Makiguchi Y, Sakamoto H, Hinoda Y, Imai K. A case of Sjogren's syndrome associated with inflammatory pseudotumor of the liver. *Nihon Rinsho Meneki Gakkai Kaishi* 1998; **21**: 226-233
- 6 Rai T, Ohira H, Tojo J, Takiguchi J, Shishido S, Sato Y, Nozawa Y, Masuda T. A case of hepatic inflammatory pseudotumor with primary biliary cirrhosis. *Hepatol Res* 2003; **26**: 249-253
- 7 Miyaguchi S, Ebinuma H, Imaeda H, Nitta Y, Watanabe T, Saito H, Ishii H. A novel treatment for refractory primary biliary cirrhosis? *Hepatogastroenterology* 2000; **47**: 1518-1521
- 8 Anthony PP. Inflammatory pseudotumour (plasma cell granuloma) of lung, liver and other organs. *Histopathology* 1993; **23**: 501-503
- 9 Ogawa T, Yokoi H, Kawarada Y. A case of inflammatory pseudotumor of the liver causing elevated serum CA19-9 levels. *Am J Gastroenterol* 1998; **93**: 2551-2555
- 10 Nakama T, Hayashi K, Komada N, Ochiai T, Hori T, Shioiri S, Tsubouchi H. Inflammatory pseudotumor of the liver diagnosed by needle liver biopsy under ultrasonographic tomography guidance. *J Gastroenterol* 2000; **35**: 641-645
- 11 Sakai M, Ikeda H, Suzuki N, Takahashi A, Kuroiwa M, Hirato J, Hatakeyama Si, Tsuchida Y. Inflammatory pseudotumor of the liver: case report and review of the literature. *J Pediatr Surg* 2001; **36**: 663-666
- 12 Sakai T, Shiraki K, Yamamoto N, Kawakita T, Ohmori S, Itoh I, Nakano T, Yasuda M, Yamakado K, Takeda K, Yagi S, Yamagiwa K, Yokoi H, Noguchi T, Uemoto S. Diagnosis of inflammatory pseudotumor of the liver. *Int J Mol Med* 2002; **10**: 281-285
- 13 Narla LD, Newman B, Spottswood SS, Narla S, Kolli R. Inflammatory pseudotumor. *Radiographics* 2003; **23**: 719-729
- 14 Jais P, Berger JF, Vissuzaine C, Paramelle O, Clays-Schouman E, Potet F, Mignon M. Regression of inflammatory pseudotumor of the liver under conservative therapy. *Dig Dis Sci* 1995; **40**: 752-756

- 15 **Di Vita G**, Soresi M, Patti R, Carroccio A, Leo P, Franco V, Montalto G. Concomitant inflammatory pseudotumor of the liver and spleen. *Liver* 2001; **21**: 217-222
- 16 **Borgonovo G**, Razzetta F, Varaldo E, Cittadini G, Ceppa P, Torre GC, Mattioli F. Pseudotumor of the liver: a challenging diagnosis. *Hepatogastroenterology* 1998; **45**: 1770-1773
- 17 **Yoon KH**, Ha HK, Lee JS, Suh JH, Kim MH, Kim PN, Lee MG, Yun KJ, Choi SC, Nah YH, Kim CG, Won JJ, Auh YH. Inflammatory pseudotumor of the liver in patients with recurrent pyogenic cholangitis: CT-histopathologic correlation. *Radiology* 1999; **211**: 373-379
- 18 **Hsu CH**, Lee CM, Lin SY. Inflammatory pseudotumor resulting from foreign body in abdominal cavity detected by FDG PET. *Clin Nucl Med* 2003; **28**: 842-844
- 19 **Standiford SB**, Sobel H, Dasmahapatra KS. Inflammatory pseudotumor of the liver. *J Surg Oncol* 1989; **40**: 283-287
- 20 **Tzioufas AG**. B-cell lymphoproliferation in primary Sjogren's syndrome. *Clin Exp Rheumatol* 1996; **14 Suppl 14**: S65-S70
- 21 **Anaya JM**, McGuff HS, Banks PM, Talal N. Clinicopathological factors relating malignant lymphoma with Sjogren's syndrome. *Semin Arthritis Rheum* 1996; **25**: 337-346
- 22 **Terpos E**, Angelopoulou MK, Variami E, Meletis JC, Vaiopoulos G. Sjogren's syndrome associated with multiple myeloma. *Ann Hematol* 2000; **79**: 449-451
- 23 **Uetsuji S**, Nakagawa A, Kwon AH, Komada H, Imamura A, Kamiyama Y. Inflammatory pseudotumor of the liver: report of a case and review of the literature. *Surg Today* 1996; **26**: 517-521
- 24 **Noi I**, Loberant N, Cohen I. Inflammatory pseudotumor of the liver. *Clin Imaging* 1994; **18**: 283-285

S- Editor Wang J L- Editor Zhang JZ E- Editor Liu WF