ANTICANCER RESEARCH *41*: 2727-2732 (2021)
doi:10.21873/anticanres.15054

# Hepatic Inflammatory Pseudotumor Mimicking Malignant Tumor With Rare Onset of Intra-abdominal Hemorrhage

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**Abstract.** *Background: Hepatic inflammatory pseudotumor (HIPT) is an uncommon benign tumor-like mass that mimics malignant tumors. Case Report: A 73-year-old man was admitted with severe epigastric pain and high fever. He had received choledocojejunostomy. Enhanced computed tomography showed a 76 mm, heterogeneous, gradual enhanced low-density mass in the caudate lobe and hyperdense fluid was detected around the mass. Based on the diagnosis of hemorrhage from a hypervascular malignant liver tumor, chemoembolization was conducted. Antibiotics (Meropenem) were administered for 2 weeks, and methylprednisolone (125 mg) was administered twice as a premedication for chemoembolization. After the 2nd chemoembolization, rapid tumor shrinkage was observed and the inflammatory changes gradually disappeared. The tumor was finally diagnosed as fibrohistiocytic type HIPT with an ultrasound-guided percutaneous tumor biopsy. The diameter of the liver tumor decreased to 15 mm and intra-abdominal hemorrhage disappeared in 3 months. Conclusion: Development of HIPT can be associated with intra-abdominal hemorrhage.*

Hepatic inflammatory pseudotumor (HIPT) is an uncommon benign tumor-like mass that is difficult to diagnose correctly because it mimics other malignant liver tumors (1-4). Although its etiology and pathogenesis are not clearly established, it has been suggested that bacterial or viral infections, as well as autoimmune reactions, may play an important role in the development HIPT. Even though HIPT patients can achieve regression spontaneously or after administration of antibiotics or steroids, the treatment of choice is still surgical resection especially for patients with severe symptoms, since these raise suspicion for malignancies less responsive to medical treatment (3, 4). To avoid unnecessary operations, needle tumor biopsy or cytology is sometimes recommended; however, iatrogenic seeding of tumor cells and misdiagnosis can occur (3, 5).

Almost all patients with HIPT are symptomatic at presentation with the most common symptoms being fever (49%), abdominal pain (48%), and fatigue/weight loss (37%) (3, 4). Other symptoms include gastrointestinal discomfort, jaundice, weakness, and muscle pain. A previous report discusses a unique case of HIPT with tarry stool at presentation (6). Intra-biliary bleeding from HIPT was suggested, but no definitive evidence was seen. Since it is a closely related disease to HIPT, that patient with hepatic IgG4-related IPT experienced rupture with hemorrhage and was treated with liver resection (7).

Hypervascular liver tumors tend to rupture and cause hemorrhage in patients, whether they are malignant (*e.g.*, hepatocellular carcinoma, liver metastases) or benign (*e.g.*, adenoma, hemangioma, focal nodular hyperplasia) (8). Other rare causes of hemorrhage include liver abscesses, parasitic and nonparasitic cysts, and hepatic peliosis. This is because the rapid growth of liver tumors can cause degeneration and cystic necrosis leading to hemorrhage. The first-line treatment for intra-abdominal or intra-tumoral bleeding caused by malignant liver tumors is transarterial chemoembolization (TACE) (9).

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*Key Words:* Hepatic inflammatory pseudotumor, intra-abdominal hemorrhage, transarterial chemoembolization, antibiotics, methylprednisolone.

To the best of our knowledge, no reports have described intra-abdominal bleeding as a presenting characteristic of typical HIPT. In this study, we report a HIPT patient diagnosed by needle tumor biopsy presenting spontaneous regression.

## Case Report

A 73-year-old man consulted a primary care physician for severe epigastric pain with a 38˚C fever for 3 days in August 2020. Computed tomography (CT) scan revealed a large hepatic tumor with intra-abdominal hemorrhage. He was transported to our hospital as an emergency case. He had a surgical history of open cholecystectomy due to acute cholecystitis in 2007 and choledocojejunostomy for bile duct stenosis in 2011. He had no existing diseases with a tendency for bleeding and no history of taking anticoagulants. Plain CT image on admission showed a 76×71 mm heterogeneous mass in the caudate lobe together with a hyperdense fluid (60×42×23 mm in size and Hounsfield unit of 60) in the subcapsular portion of the liver and inside the omental bursa, which was likely a tumor hemorrhage (Figure 1A, B). Dynamic CT showed a gradually increasing heterogeneous arterial enhancement without significant washout, together with hypodense areas of necrosis (Figure 1C, D). $^{18}$F-Fluorodeoxyglucose positron emission tomography/CT fusion image showed strong uptake in the liver tumor (standardized uptake value max 6.8) and a suspicious hematoma (standardized uptake value max 7.3) inside the omental bursa (Figure 2A, B). The tumor was described as heterogeneous and hyperintense on T2-weighted Magnetic resonance (MR) image and had scattered areas of very high intensity in diffusion-weighted MR image. Further heterogeneous enhancement was seen in the arterial and hepatobiliary phases of gadolinium d-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced MR images (Figure 2C-F).

On admission, inflammation parameters were remarkably elevated; white blood cell was $10.5\times10^3$/μl (normal: 3.3-$8.6\times10^3$/μl), neutrophil count was 91.8% (38-56%), C-reactive protein was 28.4 mg/dl, (≤0.14 mg/dl), and procalcitonin was 10.3 ng/ml (≤2.0 ng/ml). Since the patient presented with a high bacterial inflammatory status, antibiotics (meropenem 3 g per day) were immediately administered, and this continued for 2 weeks. The patient's hemoglobin level decreased from 15.5 g/dl before the onset of bleeding to as low as 12.5 g/dl after admission. Liver enzyme levels were also mildly elevated; AST was 68 IU/l (13-30 IU/l), while ALT was 77 IU/l (10-42 IU/l). Prothrombin activity was slightly decreased, at 64.5% (70%-140%). The patient was negative for both hepatitis B virus surface antigen and hepatitis C virus antibody. The levels of tumor markers were within normal ranges, except for the protein induced by the absence of vitamin K or antagonist II, 93 mAU/ml (≤40 mAU/ml).

Based on the diagnosis of hemorrhage from an unknown hypervascular liver neoplasm, TACE was performed twice. While conducting TACE, however, active bleeding was not confirmed. Excessive embolization of the liver parenchyma was avoided due to the patient's prior choledocojejunostomy. Furthermore, the right hepatic artery was occluded due to the prior surgical procedure. Cisplatin suspended in lipiodol (10) was administered *via* a collateral artery using a balloon-occluded microcatheter. Methylprednisolone (125 mg) was administered twice for every TACE as a premedication. The clinical course after these treatments was good. Abdominal pain and inflammatory reaction on a blood test gradually improved. Details of treatment and changes in inflammatory markers are shown in Figure 3. Remarkable tumor shrinkage was seen, together with accumulation of lipiodol in plain CT 4 days after the 2nd TACE (Figure 1E). After rapid tumor shrinkage, since there was less suspicion for a malignant tumor, an ultrasound-guided percutaneous tumor biopsy was conducted. In addition, we tried to obtain specimen not only from the liver tumor but also from the intra-abdominal dispersed lesions *via* a laparoscopic approach, because both lesions showed high uptake of $^{18}$F-FDG-PET/CT fusion image. Unfortunately, due to excessive intra-abdominal adhesions due to the patient's previous operations, we were only able to perform the 2nd tumor biopsy under artificial ascites storage.

On microscopic examination, the specimen showed prominent fibrosis and an infiltration of chronic inflammatory cells such as macrophages and lymphocytes (Figure 4A), and also few multinucleated giant cells were detected (Figure 4B). Atypical hepatocytes were not detected in the specimen. Immunohistochemical analyses detected many foamy cells and myofibroblasts and few multinucleated giant cells in the lesion (Figure 4C, D). Inflammatory myofibroblastic tumor (IMT) and IgG4-related disease were both ruled out because no anaplastic lymphoma kinase-positive tumor cells and few IgG4-positive cells were detected (11). These findings suggest an inflammatory pseudotumor, fibrohistiocytic type (12). Finally, the liver tumor was diagnosed as HIPT.

He was dismissed from the hospital 20 days after admission and is doing well without complaints. The liver tumor diameter decreased to 15×13 mm after 3 months (Figure 1F), and the intra-abdominal dispersed lesions also decreased. There were no data suggesting recurrence of inflammation.

## Discussion

To the best of our knowledge, this is the first reported case of HIPT with unexpected intra-abdominal hemorrhage. A high inflammatory status was seen at the time of emergent admission, but he also had a hypervascular solid tumor without an abscess-like cystic area together with intratumoral

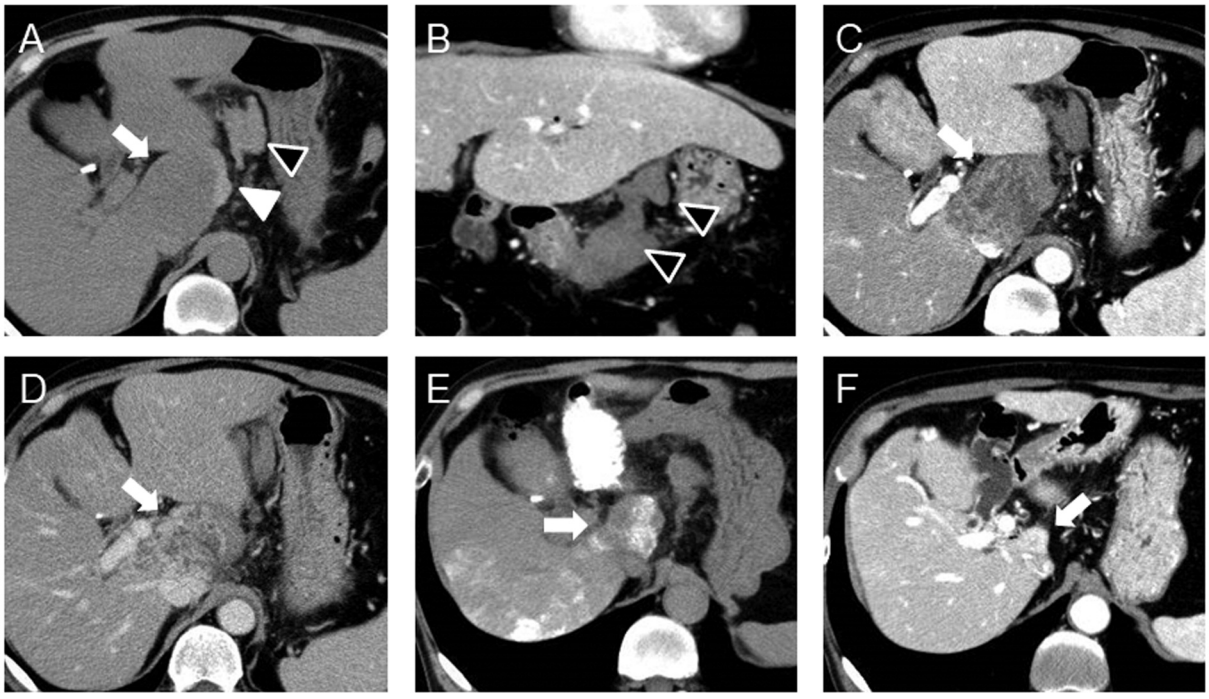


Figure 1. *Serial abdominal computed tomography (CT) images. (A) Plain, (B) coronal portal venous phase, (C) arterial phase, and (D) delayed phase. Plain CT 4 days after the 2nd transarterial chemoembolization (TACE) (E). Follow-up CT after 3 months in portal venous phases (F). The liver tumor is indicated with arrows. The subcapsular hemorrhage and hemorrhage inside the omental bursa cavity are indicated as high-density areas, pointed out with white and black arrowheads, respectively (A). The tumor was gradually enhanced (B, C). Plain CT after TACE showed heterogeneous hyperdensity representing lipiodol deposition (D). Follow-up CT after 3 months showed homogeneous enhancement of the tumor in arterial and portal venous phases (E, F).*

hemorrhage. Due to the severe inflammation, broad-spectrum antibiotics were systemically administered for 2 weeks after admission. The patient had previously undergone choledocojejunostomy for bile duct stenosis and was thought to be at high risk for HIPT. Bile duct stent placement and choledocojejunostomy are well-known risk factors for HIPT formation (4, 13, 14). Thus far, only a few reported cases of HIPT were initially diagnosed as intra-abdominal bleeding. One patient had gastrointestinal bleeding probably *via* the bile duct due to HIPT (6). Another patient had a ruptured hepatic IgG4-related IPT with subcapsular hemorrhage (7), while two patients with gastric and intestinal inflammatory myofibroblastic tumors had presented with an acute-onset spontaneous hemoperitoneum due to tumor rupture (15, 16).

Since undiagnosed hypervascular malignant liver tumors sometimes present with a hemoperitoneum, we performed emergent TACE to stop the bleeding. Transarterial embolization effectively induces hemostasis in the acute stage with a success rate of 53%-100% (9). We performed TACE procedures twice, using cisplatin suspended in lipiodol as an embolic material together with methylprednisolone as premedication. Immediately after adequate tumor embolization by the 2nd TACE, the tumor showed prompt shrinkage and the inflammatory changes gradually disappeared. Unfortunately, it is unclear, which intervention was effective and how effective it was. In a review of the literature for HIPT, 53 patients were treated with medical therapy, approximately 50% were treated with antibiotics, 15% received steroids, and 33% received no treatment. Unfortunately, initial medical therapy failed in five patients (3). Another multicenter study (4) demonstrated that 10 (22%) patients underwent surgical resection and the remaining 35 (78%) patients were treated conservatively. No recurrence was observed after surgical resection during the follow-up period (1 to 48 months). In all patients who received conservative treatment, complete remission or size reduction was observed during a median follow-up of 7.4 months (1 to 192 months).

Despite recent advances in imaging techniques, it is difficult to differentiate HIPT from other liver tumors such as atypical HCC, intrahepatic cholangiocarcinoma, liver metastases, various sarcomas, or liver abscess. Imaging studies of HIPT vary according to its inflammatory stage (17). The most common comprehensive initial diagnosis based on laboratory and imaging findings was liver malignancy (51.1%), followed by liver abscess (17.8%) (4). On CT, our patient showed an

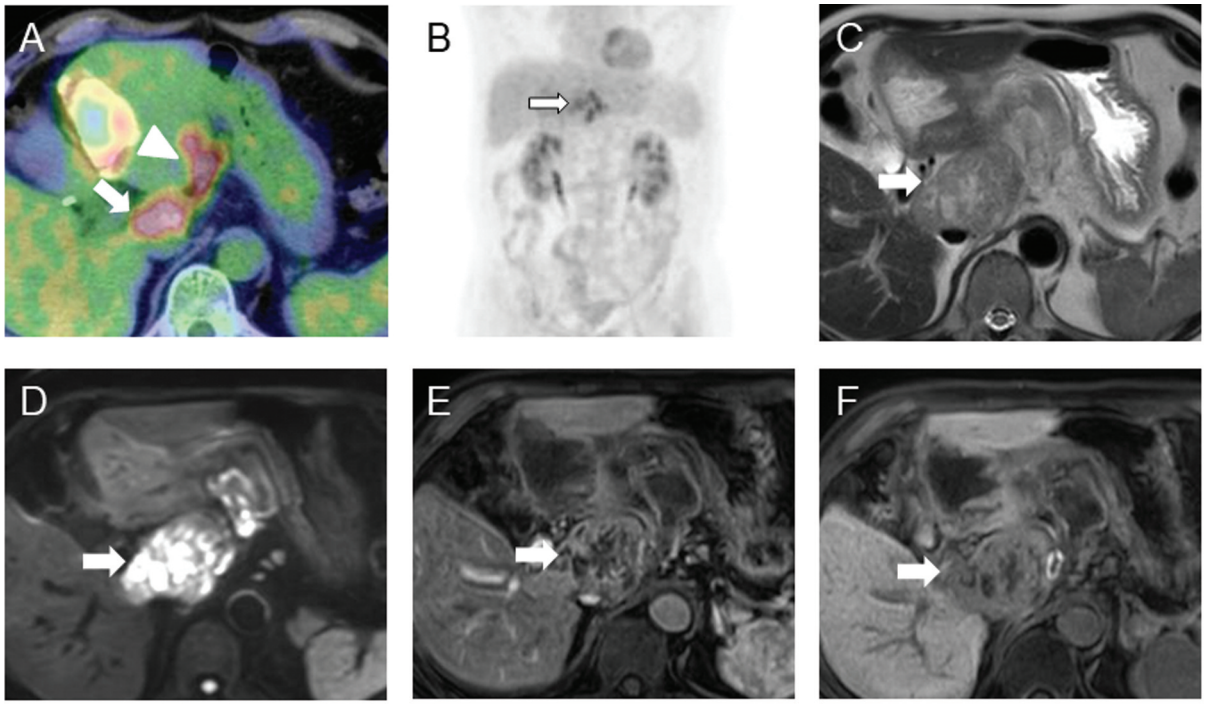


Figure 2. *$^{18}$F-fluorodeoxyglucose positron emission tomography /CT fusion and magnetic resonance images. Axial $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT fusion image (A) and 3D-maximum intensity projection image (B). Magnetic resonance (MR) images. (C) T2-weighted MR image; (D) diffusion-weighted MR image; arterial (E) and hepatobiliary (F) phases of the gadolinium d-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced MR images.*

enhanced area suspected to be a solid component, which was different from a typical abscess together with hemorrhage from the liver tumor. On magnetic resonance imaging (MRI), the tumor showed a heterogeneous hyperintensity on T2-weighted imaging relative to the liver parenchyma. Diffusion-weighted images showed that the lesions had very high intensity with an apparent diffusion coefficient value of $1{,}100\times10^{-3}$ $mm^2/s$. FDG-PET image showed high uptake in the primary tumor and hematomas inside the omental bursa. These findings were more suspicious for malignant tumors rather than benign or inflammatory ones. Even contrast-enhanced ultrasound was insufficient in distinguishing HIPT from HIPT-like hepatic malignancies including intrahepatic cholangiocarcinoma and liver metastases (18). Recently, a unique paper was published about differentiating a diagnosis of HIPT from colorectal liver metastases *via* MRI (19). In size-matched patients, reliable gadoxetate disodium-enhanced MRI features for distinguishing HIPT from colorectal liver metastases included 1) a central hypointensity with a relatively peripheral hyperintensity in the hepatobiliary phase, 2) higher lesion-to-liver signal intensity ratio in the hepatobiliary phase, and 3) lower lesion-to-liver signal intensity ratio on diffusion-weighted imaging. These findings can be caused by rich inflammatory cell infiltration in the central area and intense fibrous tissue in the peripheral area of IPT (20, 21).

For suspicious malignant tumors, especially primary or secondary adenocarcinoma of the liver, tumor biopsy should be avoided (22). In our patient, after determining that a non-malignant tumor was more likely, two ultrasound-guided tumor biopsies were performed. Thereafter, the tumor was histologically diagnosed as HIPT with no malignant features. The tumor gradually decreased in maximal diameter, from 65 mm to 15 mm, and the hemoperitoneum completely vanished after 3 months. Inflammation changes in laboratory data also normalized in 1 month.

In conclusion, HIPT can develop with intra-abdominal hemorrhage. Special attention is required for patients with inflammatory changes and a history of bile duct stent placement and choledocojejunostomy. Tumor biopsy is recommended when the possibility of a malignant tumor is low.

## Conflicts of Interest

All Authors have no conflicts of interest to declare in relation to this article.

## Authors' Contributions

Manuscript writing: Beppu T, Yamamura K. Substantial contributions to conception: Motohara T, Miyamaoto H, Miyamura

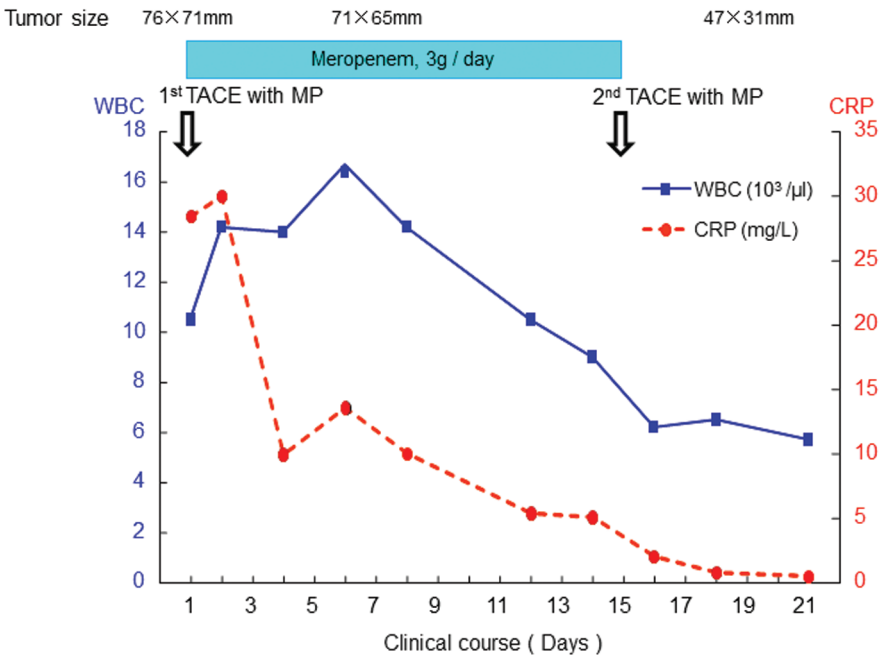


Figure 3. *Details of treatment and changes in inflammatory markers and tumor size. TACE: Transarterial chemoembolization; MP: methylprednisolone; WBC: white blood cell; CRP: C-reactive protein.*

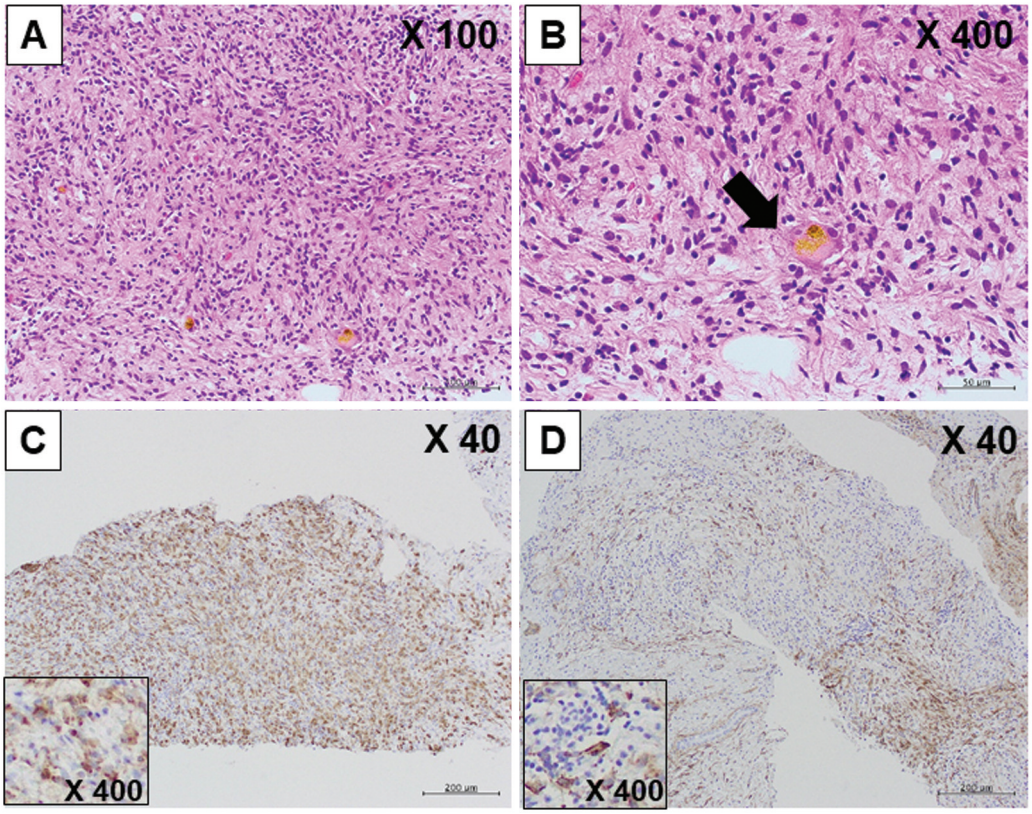


Figure 4. *Microscopic findings. (A) histopathological findings at high magnification, (×100), (B) and very high magnification (×400). Many foamy cells and multinucleated giant cells (arrow) were observed (B). Immunohistochemical staining at high (×40) and very high magnification (×400) for CD68 (C) and smooth muscle actin (D).*

S. Technical supports and interpretation: Beppu T, Yamamura K, Yuki H, Oda E, Sato N, Akahoshi S. Histopathological diagnosis: Onishi K, Komohara Y.

## References


1 Li GH, Li JQ and Lin YZ: Inflammatory pseudotumor of the liver. J Surg Oncol *42(4)*: 244-248, 1989. PMID: 2687584. DOI: 10.1002/jso.2930420409

2 Kafeel G and Telesinghe PU: Inflammatory pseudotumour of the liver. J Clin Pathol *50(4)*: 352-353, 1997. PMID: 9215157. DOI: 10.1136/jcp.50.4.352

3 Goldsmith PJ, Loganathan A, Jacob M, Ahmad N, Toogood GJ, Lodge JP and Prasad KR: Inflammatory pseudotumours of the liver: a spectrum of presentation and management options. Eur J Surg Oncol *35(12)*: 1295-1298, 2009. PMID: 19515527. DOI: 10.1016/j.ejso.2009.04.003

4 Park JY, Choi MS, Lim YS, Park JW, Kim SU, Min YW, Gwak GY, Paik YH, Lee JH, Koh KC, Paik SW and Yoo BC: Clinical features, image findings, and prognosis of inflammatory pseudotumor of the liver: a multicenter experience of 45 cases. Gut Liver *8(1)*: 58-63, 2014. PMID: 24516702. DOI: 10.5009/gnl.2014.8.1.58

5 Bakoyiannis A, Delis S, Triantopoulou C and Dervenis C: Rare cystic liver lesions: a diagnostic and managing challenge. World J Gastroenterol *19(43)*: 7603-7619, 2013. PMID: 24282350. DOI: 10.3748/wjg.v19.i43.7603

6 Zhang Y, Lu H, Ji H and Li Y: Inflammatory pseudotumor of the liver: A case report and literature review. Intractable Rare Dis Res *4(3)*: 155-158, 2015. PMID: 26361568. DOI: 10.5582/irdr.2015.01021

7 Mulki R, Garg S, Manatsathit W and Miick R: IgG4-related inflammatory pseudotumour mimicking a hepatic abscess impending rupture. BMJ Case Rep *2015*: bcr2015211893, 2015. PMID: 26392451. DOI: 10.1136/bcr-2015-211893

8 Caremani M, Tacconi D and Lapini L: Acute nontraumatic liver lesions. J Ultrasound *16(4)*: 179-186, 2013. PMID: 24432172. DOI: 10.1007/s40477-013-0049-2

9 Sahu SK, Chawla YK, Dhiman RK, Singh V, Duseja A, Taneja S, Kalra N and Gorsi U: Rupture of hepatocellular carcinoma: a review of literature. J Clin Exp Hepatol *9(2)*: 245-256, 2019. PMID: 31024207. DOI: 10.1016/j.jceh.2018.04.002

10 Beppu T, Ohara C, Yamaguchi Y, Ichihara T, Yamanaka T, Katafuchi S, Ikei S, Mori K, Fukushima S and Nakano M: A new approach to chemoembolization for unresectable hepatocellular carcinoma using aclarubicin microspheres in combination with cisplatin suspended in iodized oil. Cancer *68(12)*: 2555-2560, 1991. PMID: 1657361. DOI: 10.1002/1097-0142(19911215)68:12<2555::aid-cncr2820681204>3.0.co;2-8

11 Arora K, Rivera M, Ting DT and Deshpande V: The histological diagnosis of IgG4-related disease on small biopsies: challenges and pitfalls. Histopathology *74(5)*: 688-698, 2019. PMID: 30408214. DOI: 10.1111/his.13787

12 Zen Y, Fujii T, Sato Y, Masuda S and Nakanuma Y: Pathological classification of hepatic inflammatory pseudotumor with respect to IgG4-related disease. Mod Pathol *20(8)*: 884-894, 2007. PMID: 17571078. DOI: 10.1038/modpathol.3800836

13 Horiuchi R, Uchida T, Kojima T and Shikata T: Inflammatory pseudotumor of the liver. Clinicopathologic study and review of the literature. Cancer *65(7)*: 1583-1590, 1990. PMID: 2155699. DOI: 10.1002/1097-0142(19900401)65:7<1583::aid-cncr2820650722>3.0.co;2-l

14 Zhao J, Olino K, Low LE, Qiu S and Stevenson HL: Hepatic inflammatory pseudotumor: an important differential diagnosis in patients with a history of previous biliary procedures. ACG Case Rep J *6(1)*: e00015, 2019. PMID: 31598534. DOI: 10.14309/crj.0000000000000015

15 Park SH, Kim JH, Min BW, Song TJ, Son GS, Kim SJ, Lee SW, Chung HH, Lee JH and Um JW: Exophytic inflammatory myofibroblastic tumor of the stomach in an adult woman: a rare cause of hemoperitoneum. World J Gastroenterol *14(1)*: 136-139, 2008. PMID: 18176977. DOI: 10.3748/wjg.14.136

16 Cholvi-Calduch R, Fernández-Moreno MC, Díaz-Tobarra M and Calvete-Chornet J: Hemoperitoneum secondary to perforated inflammatory myofibroblastic tumor: A case report of an unusual complication. Rev Esp Enferm Dig *108(1)*: 51-52, 2016. PMID: 26765239.

17 Murakami T and Tsurusaki M: Hypervascular benign and malignant liver tumors that require differentiation from hepatocellular carcinoma: key points of imaging diagnosis. Liver Cancer *3(2)*: 85-96, 2014. PMID: 24944999. DOI: 10.1159/000343864

18 Kong WT, Wang WP, Shen HY, Xue HY, Liu CR, Huang DQ and Wu M: Hepatic inflammatory pseudotumor mimicking malignancy: the value of differential diagnosis on contrast enhanced ultrasound. Med Ultrason *23(1)*: 15-21, 2021. PMID: 32905565. DOI: 10.11152/mu-2542

19 Ichikawa S, Motosugi U, Suzuki T, Shimizu T and Onishi H: Imaging features of hepatic inflammatory pseudotumor: distinction from colorectal liver metastasis using gadoxetate disodium-enhanced magnetic resonance imaging. Abdom Radiol (NY) *45(8)*: 2400-2408, 2020. PMID: 32468212. DOI: 10.1007/s00261-020-02575-7

20 Ahn K, Kang K, Kim Y, Lim T, Jung H, Kang Y and Kwon J: Inflammatory pseudotumors mimicking intrahepatic cholangiocarcinoma of the liver; IgG4-positivity and its clinical significance. Journal of Hepato-Biliary-Pancreatic Sciences *19(4)*: 405-412, 2019. DOI: 10.1007/s00534-011-0436-z

21 Chang SD, Scali EP, Abrahams Z, Tha S and Yoshida EM: Inflammatory pseudotumor of the liver: a rare case of recurrence following surgical resection. J Radiol Case Rep *8(3)*: 23-30, 2014. PMID: 24967025. DOI: 10.3941/jrcr.v8i3.1459

22 Akahoshi S, Yamamura K, Sato N, Oda E, Kinoshita K, Yuki H, Motohara T, Deguchi A, Komohara Y and Beppu T: A hepatic sclerosed hemangioma with drastic changes in contrast-enhanced ultrasonography. Clin J Gastroenterol *13(6)*: 1252-1257, 2020. PMID: 32705537. DOI: 10.1007/s12328-020-01194-5


*Received March 1, 2021*
*Revised April 18, 2021*
*Accepted April 19, 2021*